Clinical Research
Faculty of Medicine
University of Helsinki

TREATMENT AND COMPLICATIONS OF JUVENILE IDIOPATHIC ARTHRITIS-RELATED UVEITIS

Sanna Leinonen

DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, at the Helsinki University Hospital, Helsinki, Finland, on the 27th of November, 2020 at 12 o'clock.

Helsinki 2020

Supervisors:

Kristiina Aalto, MD, PhD
Docent
Department of Paediatrics
University of Helsinki
Helsinki, Finland

Tero Kivelä, MD, PhD, FEBO
Professor of Ophthalmology
Department of Ophthalmology
University of Helsinki
Helsinki, Finland

Kaisu Kotaniemi, MD, PhD
Docent
Department of Ophthalmology
University of Helsinki
Helsinki, Finland

Reviewers:

Bahram Bodaghi, MD, PhD, FEBO
Professor of Ophthalmology
Department of Ophthalmology
Sorbonne University
Paris, France

Tuulikki Sokka-Isler, MD, PhD
Professor of Rheumatology
Department of Rheumatology
University of Eastern Finland
Kuopio, Finland

Opponent:

Manfred Zierhut, MD, PhD
Professor of Ophthalmology
Department of Ophthalmology
University of Tuebingen
Tuebingen, Germany

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

ISBN 978-951-51-6796-5 (pbk.)
ISBN 978-951-51-6797-2 (PDF)

Unigrafia
Helsinki 2020

To my friends and family

ABSTRACT

Juvenile idiopathic arthritis and related uveitis is a persistent childhood-onset inflammatory disease affecting one or more joints and one or both eyes. The origin of this disease is unknown.

In the eye, the inflammation can cause vision impairing complications such as cataract and glaucoma as well as oedema and scarring of the central retina. The focus of uveitis treatment is to improve the visual prognosis by controlling the inflammation. Topical glucocorticoids reduce inflammation in the eye but do not control the systemic joint disease, and they tend to induce cataract formation, high intraocular pressure and related glaucoma, which is why children with juvenile idiopathic arthritis-related uveitis are treated with systemic antirheumatic drugs. These drugs reduce the inflammation in the eyes and the joints, they improve visual prognosis and they are not associated with further ocular complications.

This study focuses on the variables contributing to treatment success when managing the inflammation and complications of juvenile idiopathic arthritis-related uveitis.

The first study showed that antirheumatic treatment might improve the results of glaucoma surgery in juvenile idiopathic arthritis-related uveitis. Glaucoma was better controlled in patients who were treated with TNF-inhibitors at the time of the surgery compared with patients without such drugs.

In the second study, patients experienced better control of uveitis when methotrexate was combined with adalimumab than adalimumab-treated patients without methotrexate.

The third study concluded that if oedema of central retina does not respond to antirheumatics and systemic glucocorticoids, a sustained-release glucocorticoid implant may help in controlling the oedema and improving visual acuity.

In the fourth study, better control of inflammation prior to cataract surgery was associated with a better postoperative visual outcome. The median visual acuity remained high among the patients with good control of uveitis 3 to 12 months preoperatively.

In summary, a more successful treatment outcome in anterior uveitis related to juvenile idiopathic arthritis can be achieved with systemic antirheumatic drugs combined with meticulous control of inflammation.

ABSTRACT IN FINNISH

Lastenreuma ja siihen liittyvä uveiitti eli suonikalvoston tulehdus on lapsuusiässä alkava pitkäaikainen sairaus, jossa yksi tai useampi nivel ja toinen tai molemmat silmät tulehtuvat. Taudin alkusyy on tuntematon.

Pitkittynyt suonikalvoston tulehdus johtaa näköä heikentäviin seurauksiin kuten kaihiin, glaukoomaan ja verkkokalvon tarkan näön alueen turvotukseen ja arpeutumiseen. Keskeistä on rajoittaa tulehdusta glukokortikoidihoidolla ja reumalääkkeillä, jotta näkö pysyisi mahdollisimman hyvänä. Glukokortikoidihoito vähentää suonikalvoston tulehdusta, mutta aiheuttaa samalla kaihia sekä silmänpaineen nousua ja siihen liittyvää sokeuttavaa glaukoomaa. Sen sijaan reumalääkkeet rajoittavat sekä nivel- että suonikalvoston tulehdusta. Reumalääkkeiden tiedetään parantavan lastenreumaa sairastavan lapsen näön pitkän ajan ennustetta eivätkä ne aiheuta kaihia tai glaukoomaa. Näistä syistä lastenreumaa sairastavia uveiittilapsia ja -nuoria kannattaa hoitaa ensisijaisesti reumalääkityksillä.

Tämän tutkimuksen tarkoituksena oli selvittää, mitkä tekijät vaikuttavat lastenreumaan liittyvän suonikalvoston tulehduksen hoidon onnistumiseen.

Ensimmäinen osatyö keskittyi glaukooman leikkaushoitoon lapsilla, joilla on lastenreuma ja siihen liittyvä suonikalvoston tulehdus. Leikkauksen painetta alentava vaikutus oli pitkäaikaisempi, jos leikattava potilas käytti biologista TNF-salpaajalääkitystä leikkaushetkellä.

Toisessa osatyössä tarkasteltiin adalimumabi-reumalääkkeen tehoa suonikalvoston tulehduksen hoidossa yksin käytettynä tai osana yhdistelmälääkitystä. Tässä osatyössä todettiin, että lääkityksen teho oli parempi, jos lapsi käytti adalimumabia yhdessä metotreksaatin kanssa kuin ilman metotreksaattia.

Kolmas osatyö osoitti, että silmänsisäisesti asetettu pitkävaikutteinen glukokortikoidi-istute vähensi verkkokalvoturvotusta, jos reumalääke tai glukokortikoidihoito suun kautta ei ollut parantanut turvotusta.

Neljännessä osatyössä todettiin, että kaihileikkauksen tulokset olivat parempia silmissä, joissa oli vähemmän tulehdusta. Näöntarkkuus säilyi hyvänä silmissä, joissa suonikalvoston tulehdus oli ollut lievempi 3-12 kuukauden ajan ennen leikkausta.

Tämän ja aiempien tutkimusten perusteella voidaan päätellä, että tulehduksen huolellinen rajoittaminen ja reumalääkkeiden aktiivinen käyttö parantaa lastenreumaan liittyvän suonikalvoston tulehduksen hoitotuloksia.

ACKNOWLEDGEMENTS

This study was carried out in the Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland during years 2014-2020.

I owe a debt of gratitude to my supervisor, docent Kaisu Kotaniemi, MD, who has laid tremendous foundations for uveitis care and research in Finland. Her wealth of clinical knowledge and systematic approach to patient care guided me through my research and my clinical work alike.

I am also deeply indebted to my supervisor, professor Tero Kivelä, MD, who guided me through this research with elegance and never-ending patience. I am very fortunate to have worked with an intellect of his caliber.

The study was planned with a multidisciplinary approach in mind, especially combining ophthalmological uveitis care with paediatric rheumatology. My gratitude goes to my third supervisor, docent Kristiina Aalto, MD, for enabling such a collaboration and for her encouragement and trust in me during the past 6 years.

I am thankful for docent Anna Majander, MD, who helped me in launching this research in 2014 and has supported my research pursuits ever since. I value your scientific and clinical expertise, and your friendship.

I wish to thank docent Kari Krootila, MD, and professor Ilkka Immonen, MD, for their collaboration, expertise and trust in me when I proceeded to study the patients they had expertly operated on.

I wish to recognise docent Jukka Moilanen, MD, and docent Erna Kentala, MD, the present and former Head of Department of Ophthalmology, respectively, and Päivi Lindahl, MD, the Director of the Paediatric Ophthalmology Service.

Special thanks to my colleague, friend and my primary consultant in the field of Paediatric Rheumatology, Johanna Kärki, MD, for her continuous support through good times and especially during the rough times. I appreciate your work moral, expertise and friendship.

To all my friends who have been part of my journey in research, ophthalmology and life, I appreciate your support and friendship throughout these years: Satu, Mira, Hanna-Mari, Mari, Veera, Maria, Heli, Anniina, Terhi, Kate, Claire, Ulrike, Stina, Mel, Jo, and to my very best friend Jennifer, who keeps me in check when I am proceeding with too much work, unhealthy habits, or other stupidities; I love you and I am lucky to have you in my life.

My parents, Eeva and Jorma, my brother Jukka and sister-in-law Kaisa, deserve my deep gratitude for their love and unwavering support of all my endeavours.

This research was facilitated by my loving husband Adam who provides me with food, clean clothes, laughs, love, support, and hugs every day! Thank you, love.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications on JIA-uveitis. Their roman numbers will refer the publications in the text.

I Leinonen S, Kotaniemi K, Kivelä T, Majander A. Potential effect of tumor necrosis factor inhibitors on trabeculectomy with mitomycin C for patients with juvenile idiopathic arthritis–related uveitic glaucoma: a retrospective analysis. JAMA Ophthalmol. 2015;133(11):1323-1328.

II Leinonen ST, Aalto K, Kotaniemi KM, Kivelä TT. Anti-adalimumab antibodies in juvenile idiopathic arthritis-related uveitis. Clin Exp Rheumatol. 2017;35(6):1043-1046. Epub 2017 Nov 14.

III Leinonen S, Immonen I, Kotaniemi K. Fluocinolone acetonide intravitreal implant (Retisert®) in the treatment of sight threatening macular edema of juvenile idiopathic arthritis-related uveitis. Acta Ophthalmol. 2018;96(6):648-651.

IV Leinonen S, Kotaniemi K, Kivelä TT, Krootila K. Results 5 to 10 years after cataract surgery with primary IOL implantation in juvenile idiopathic arthritis -related uveitis. J Cataract Refract Surg. 2020 Aug;46(8):1114-1118.

ABBREVIATIONS

ADAb	antidrug antibody
ANA	antinuclear antibody
BCVA	best-corrected visual acuity in decimal notation
CI	confidence interval
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
FAI	fluocinolone acetonide implant Retisert®
HR	hazard ratio
IL-6	interleukin-6
ILAR	International League of Associations for Rheumatology
IOL	intraocular lens
IOP	intraocular pressure
JIA	juvenile idiopathic arthritis
MMC	mitomycin C
N/A	not applicable
Nd:YAG	neodymium-doped yttrium aluminum garnet
OCT	optical coherence tomography
OR	odds ratio
PCO	posterior capsular opacification
PMMA	polymethylmethacrylate
RNA	ribonucleic acid
RF	rheumatoid factor
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
Stata	Software for Statistics and Data Science
SUN	Standardization of Uveitis Nomenclature
Th	T helper cell
TNF	tumor necrosis factor

1. INTRODUCTION

Anterior uveitis related to JIA is an inflammatory disease of the eye. It is a sight-threatening condition that is asymptomatic and chronic in nature.[1–3] Systematic screening for uveitis is performed on all children who have been diagnosed with JIA.[4] Cumulative incidence of JIA-uveitis is as high as 27% in Finland.[5,6]

JIA-uveitis-related inflammation presents as leukocytes and flare in the eye.[3,7] Persistent inflammation causes structural changes such as band keratopathy, posterior synechiae, cataract, low intraocular pressure sometimes leading to phthisis bulbi, high intraocular pressure leading to secondary glaucoma, vitreous inflammatory changes, macular oedema, macular scarring, and retinal detachment.[3,7–9] Visual prognosis is poor in eyes with persistent inflammation, uveitis-related complications, intraocular surgeries for complications, and in patients with inadequate antirheumatic treatment.[9]

Severe visual loss occurs in 4-34% of eyes with JIA-uveitis.[7,9–13] The goal of treatment is to improve the long-term visual prognosis by reducing uveitis-related ocular inflammation and the occurrence of ocular complications.[9,14,15]

JIA-uveitis-related inflammation is controlled with glucocorticoids, DMARDs and biologic systemic medication.[14,15] Remission of uveitis with no inflammatory cells in the anterior chamber is preferred, but if remission is not achievable, up to 5 cells per 1 mm^2 in the slit lamp beam can be tolerated.[9,16,17]

If low-dose topical glucocorticoid treatment does not provide sufficient control of inflammation, antirheumatic therapy is added to the treatment. Methotrexate is the mainstay of DMARD therapy in JIA-uveitis. If DMARD therapy does not control the inflammation, a biologic drug is combined in the regimen. TNF inhibitors are the first choice of biologic treatment in JIA-uveitis.[14,15,18]

The most common vision-threating complications of JIA-uveitis are glaucoma and macular oedema.[13] The most common complication overall is cataract.[7,13,16,19] No general agreement exists on the best treatment protocol for treating secondary glaucoma[20–23] and macular oedema[24–27] in JIA-uveitis. Details of the surgical approach and perioperative care in cataract surgery depend on the center and the surgeon.[28–32]

This thesis focuses on the factors contributing to successful outcomes in the treatment of JIA-uveitis and related complications.

2. REVIEW OF THE LITERATURE

Uveitis is a potentially vision impairing disease that causes up to 10% of severe vision loss (BCVA ≤0.1) in the Western world.[1,2,33]

Uveitis is a heterogeneous group of diseases affecting the uveal tract, the middle layer of the eye. Uveal tract consists of three parts: the iris, the ciliary body, and the choroid. From an anatomical perspective, uveitis can predominantly affect the iris as anterior uveitis, the ciliary body as intermediate uveitis, or the choroid as posterior uveitis. Uveitis can also occur as panuveitis throughout the whole uveal tract.[33,34] The most common type of uveitis is anterior uveitis.[35] The course of uveitis can be acute, relapsing, or chronic. Uveitis can cause symptoms or it can be asymptomatic.[33,34] Uveitis can be triggered by an infection or an injury, but often the origin of inflammation remains elusive and the disease is, therefore, idiopathic.

Idiopathic uveitis can occur alone or with another recognisable autoimmune or autoinflammatory systemic disorder.[34,36] According to a Swedish population-based study, 8% of all patients with uveitis have an associated systemic disease, and only 1% of patients have an association with JIA.[35] In a Finnish population-based study by Siiskonen *et al.*, prevalence of uveitis in children <16 years of age increased from 64 to 106 per 100000 during 2008-2017. The incidence of uveitis was 14 per 100000 children. Among Finnish children, 9% of the uveitidis were infectious, 5% are posttraumatic or postoperative, 61% associate with JIA, 7% associate with some other systemic disease, and 18% have no known disease association or aetiology.[37] Although it is a rare disease entity, anterior uveitis associated with JIA is the most common type of uveitis in children in Finland.[37,38]

2.1. JIA AND UVEITIS

JIA is a chronic disease in which one or multiple joints are affected by arthritis that persists ≥6 weeks. The disease onset occurs before the age of 16 years and is of unknown origin. JIA is categorised in 7 subtypes depending on the number of affected joints and on presence of additional systemic symptoms, psoriasis, or a positive RF.[39] (Table 1)

Table 1. Classification of JIA according to ILAR criteria

Subtype	Definition
Systemic arthritis	≥1 joints affected and systemic symptoms
Oligoarthritis	1-4 joints affected at the onset
Persistent	1-4 joints affected
Extended	≥5 joints affected after the first 6 months
Polyarthritis (RF negative)	≥5 joints affected and negative RF
Polyarthritis (RF positive)	≥5 joints affected and positive RF
Psoriatic arthritis	≥1 joints affected and psoriasis
Enthesitis-related arthritis	≥1 joints affected and inflammation of an enthesitis site
Other arthritis	

In Europe, the prevalence of JIA is 70 (95% CI, 63-78) and annual incidence is 8 (95% CI, 8-9) per 100 000 children that are younger than 16 years of age. JIA is more common among girls (prevalence, 19; 95% CI, 19-21) than boys (prevalence, 11; 95% CI, 10-12).[40]

Uveitis occurs in 12-27% of children with JIA.[4–6,41] Finland has the highest reported cumulative incidence of uveitis in JIA.[5,6,41] JIA-uveitis-like anterior uveitis can occur in children also without an association with JIA.[37,42] These childhood-onset uveitidis without a known aetiology or an associated systemic disease have JIA-uveitis-like clinical features and are treated following JIA-uveitis quidelines.[37,43]

The mean onset of JIA is around 5 years of age. Patients with JIA-uveitis are significantly younger (3.2-3.8 years) at the onset of arthritis than patients with JIA without uveitis (6.2-7.0 years).[4,6] Uveitis is diagnosed at a median 6-10 months after the manifestation of arthritis. Altogether 54-73% of the JIA-uveitis diagnoses are discovered during the first year after the onset of arthritis, and 82-90% during the first 4 years.[4–6] Uveitis may also develop as late as 8-18 years after the diagnosis of JIA.[41]

Persistent oligoarthritis, extended oligoarthritis, RF-negative polyarthritis, and psoriatic arthritis have been associated with a high risk for uveitis. In a German population-based study, extended oligoarthritis had the highest cumulative rate of uveitis (19%),[4] whereas in the Nordic population, the highest cumulative rate was found among patients with juvenile psoriatic arthritis (36%).[6] Systemic-onset JIA and RF-positive JIA carry the lowest risk of uveitis, ranging from 0% to 6%.[59,83,117] (Table 2) Other risk factors for

JIA-uveitis include young age, high titers of anti-histone antibodies, and ANAs at the onset of JIA.[4–6]

Antirheumatic treatment has a protective effect against JIA-uveitis.[44,45] The hazard ratio for uveitis is 0.29 (95% CI, 0.19-0.45) with methotrexate if started within the first year of JIA. Hazard ratio for developing uveitis in JIA is as low as 0.10 (95% CI, 0.05–0.23) when the patient is treated with methotrexate and a TNF inhibitor.[45]

Table 2. Risk of uveitis in JIA by Heiligenhaus et al.4

Subgroups	*p*-value	OR (95% CI)
Systemic-onset JIA		Reference
Persistent oligoarthritis	<0.001	19 (5-78)
Extended oligoarthritis	<0.001	33 (8-137)
Polyarthritis (RF negative)	0.036	5 (1-21)
Polyarthritis (RF positive)	0.19	3 (0-22)
Enthesitis-related arthritis	0.008	7 (2-30)
Psoriatic arthritis	0.001	11 (3-48)
Other / undefined arthritis	0.001	12 (3-52)
Disease onset in years	<0.001	
Duration of disease in years	0.002	
ANA positive at diagnosis	<0.001	

Persistent inflammation of the uveal tract causes vision impairing structural complications in the uvea and adjacent structures in JIA-uveitis.[8] The vision in children with JIA-uveitis can deteriorate at such a young age and so insidiously that the child does not recognise that they do not see well.[8,46] Therefore, all children with JIA are routinely screened for uveitis.[4] Early diagnosis of uveitis before ocular complications and vision loss develop is crucial in improving the visual prognosis in JIA-uveitis.[4,8,9,47]

A modified version of the screening guideline for JIA-uveitis published by Heiligenhaus *et al.*[4] has been applied in Finland since 2014. Children with JIA and high risk of uveitis because of their young age, ANA profile, and type of arthritis are followed by an ophthalmologist every 3 months during the first 2-4 years from the onset of arthritis, and every 6-12 months thereafter. Children with low risk of uveitis are screened every 12 months from the onset of arthritis. Children whose antirheumatic therapy is discontinued are screened for uveitis at 3-6 months thereafter because a high relapse rate is suspected following the discontinuation of medication.[48] (Table 3)

Systematic screening for uveitis in JIA ends at 16 years of age. In 2020, a Nordic population-based cohort study revealed that uveitis can develop also late in the course of JIA. Uveitis developed in 2.8% (12 of 434 patients) at 8-18 years from the onset of JIA. Among these 12 patients, median age at diagnosis of uveitis was 22.9 years. At least five of them had a symptomatic course of uveitis and only one of them developed uveitis-related

complications. It remains to be seen if this discovery will change the screening guidelines for JIA-uveitis in the future.[41]

Table 3. Screening guideline for JIA-uveitis in Finland

	Oligoarthritis, extended oligoarthritis, polyarthritis RF -, psoriatic arthritis, other arthritis				
	≤6 years of age at the diagnosis			>6 years of age at the diagnosis	
Years from diagnosis (max 16 years of age)	ANA+		ANA-	ANA+	ANA-
0-2	3 months	3 months	6 months	6 months	12 months
2-4		6 months		12 months	
4-7	6 months		12 months		
>7	12 months	12 months			
	Control at 3-6 months if antirheumatic therapy is discontinued				

Enthesitis-related arthritis, polyarthritis RF+, systemic-onset arthritis
Every 12 months until 16 years of age
Control at 3-6 months if antirheumatic therapy is discontinued

2.2. IMMUNOLOGY

It is unclear which factors contribute to the induction of non-infectious, non-traumatic uveitis. The origin is either autoimmune, autoinflammatory, immune-mediated, or a combination thereof.[49] Autoimmune has been the most commonly used term when describing the nature of non-infectious, non-traumatic uveitis although there is sparse evidence for an autoimmune-specific pathophysiology in uveitis.[14,15,33]

Autoimmune diseases are driven by irregular immune recognition of organ-specific autoantigens and autoantibody and T cell driven autoreaction against the host organ tissue.[49] Immune-mediated diseases start from an inflammatory reaction triggered by an autologous damaged tissue or an external factor.[49,50] In autoinflammatory disorders, innate immune cells autoactivate against host tissue without an external trigger and despite low titers of autoantibodies and lack of a T cell driven response.[49]

Pathogenesis of uveitis has been studied in animal models. In experimental animal models, uveitis shares characteristics with both immune-mediated and autoimmune disorders.[36,50,51] Retinal antigen-specific T cells mediate experimental autoimmune uveitis in animal models, which agrees with the defining criteria of autoimmune disorders. Agreeing with an immune-mediated pathogenesis, T cells are activated by innate stimuli caused by an environmental factor such as bacterial endotoxins. T cell lineages differentiate based on the surrounding antigens and cytokines. With retinal antigens present, T cells can differentiate into uveitis-inducing retinal antigen-specific lineages. T helper cell lines Th1, Th9 and Th17 are likely uveitogenic. Th1 and Th2 seem to have a double role as pathogens and protective agents in the pathogenesis of uveitis. Without an antigen-

mediated activation, T cells can differentiate into T regulatory cells that can dampen uveitogenic T cell migration into the eye. In the eye, the activated retinal antigen-specific T cells break down the blood-retinal barrier, which, together with neutrophils and cytokines, induces uveal inflammation.[50,51] It is unknown how closely human uveitis resembles experimental uveitis in animal models. The only common factor seems to be T cells that induce experimental autoimmune uveitis while T cell-targeting drugs abatacept, cyclosporine A, mycophenolic acid, and tocilizumab can control inflammation in human uveitis.[36,49,52–56] The other two factors present in the induction of experimental animal uveitis, retinal antigens and environmental factors, are unrevealed in the pathogenesis of human uveitis.[36,49]

An autoimmune pathogenesis is uncertain in many idiopathic uveitidis including JIA-uveitis.[49] Agreeing with an autoimmune pathway, T cells seem to have a role in JIA-uveitis. JIA-uveitis-related inflammation can be treated with T cell-targeting drugs.[52,54–58] Children with JIA, those with JIA-uveitis, and those with idiopathic uveitis without JIA, have elevated serum levels of uveitogenic Th17 cells. The serum Th1/Th2 ratio, a possible marker for uveitis, is increased among patients with JIA-uveitis.[59] It is not yet known whether these changes in Th levels contribute to the pathogenesis of uveitis or are a consequence of it.[51,59] Disagreeing with an autoimmune pathogenesis, specific autoantigens have not been identified and representative experimental autoimmune animal models do not exist for JIA-uveitis. An autoinflammatory origin is also uncertain in the pathogenesis of JIA-uveitis because a key marker for autoinflammation is lack of a T cell driven inflammatory response.[51,59] Nevertheless, these findings do not rule out either autoimmunity or autoinflammation as a part of the disease process in JIA-uveitis or uveitis in general.[49]

2.2.1. TNF

TNF is a cytokine involved in controlling inflammation, anti-tumor responses, and immune system homeostasis. TNF has both anti-inflammatory and proinflammatory activities. TNF mediates inflammatory activity of T cells and structural cells such as fibroblasts, endothelial cells, and epithelial cells. It is pathogenic in many inflammatory diseases and, possibly, also protective in some inflammatory diseases. It is not clear how much TNF contributes to autoimmunity or protection against autoimmunity.[51,60]

TNF is expressed in soluble and transmembrane forms by multiple cell types integral to ocular inflammation such as Th1 and Th17 cells, monocytes, macrophages, and resident ocular cells.[51,60] TNF seems to play a major role in non-infectious uveitis and in JIA.[51,60,61] Patients with uveitis have elevated TNF levels in their peripheral serum and aqueous humour.[51,62–64] A correlation has been found between recurrent uveitis and elevated TNF serum levels.[63] In experimental animal models, TNF causes blood-retinal barrier breakdown, and anti-TNF therapy suppresses uveal inflammation.[65,66]

Patients with JIA-uveitis[15,67,68] and JIA[69,70] benefit from TNF inhibitor therapy, although no clear connection exists between TNF serum levels and

JIA, or between TNF serum levels and clinical improvement of JIA with TNF inhibitors.[61,71–73] This inconsistency highlights the lack of understanding of the inflammatory pathways and interrelations of cytokines in inflammatory diseases.[61]

2.3. VISUAL PROGNOSIS

The course of JIA-uveitis can be so severe that it may cause bilateral blindness.[7,13] The frequency of severe vision loss with BCVA ≤0.1 in eyes with JIA-uveitis ranges from 4% to 34%.[3,7,9,10,12,13,47] In a study by Angeles-Han *et al.* published in 2015, 45% of the children with JIA-uveitis had vision loss, and 18% had severe vision loss with BCVA ≤0.1 in both eyes.[13]

Risk factors for poor visual prognosis are diagnosis of uveitis concurrently with JIA, ocular complications at the time of diagnosis, high-grade uveitis, ≥3 ocular complications, intraocular surgeries during treatment, lack of antirheumatic medication, bilateral uveitis, and long disease duration.[8,9,12,13,19]

The goal of treatment in JIA-uveitis is to achieve and maintain good vision throughout life. Improved visual prognosis can be achieved by early diagnosis, good control of the inflammation, avoidance of ocular complications, and minimising the need for intraocular surgeries.[8,9,16,19]

2.4. CONTROL OF INFLAMMATION

In chronic anterior JIA-related uveitis, the likelihood of poor visual prognosis increases with increasing anterior chamber inflammatory cell count.[9,16] The risk of poor visual prognosis begins to increase markedly when the anterior chamber cell count reaches >5 cells /1 mm² in a slit lamp beam. HR for poor BCVA ≤0.1 increases from 1.15 to 6.99 when the cell count increases from ≤5 /1 mm² to >40 /1 mm² in the anterior chamber.[9]

Clinical remission defined as 0 cells /1 mm² in the anterior chamber should be pursued when treating JIA-uveitis. If remission is not achievable, no more than 1-5 cells /1 mm² should be pursued to ensure a favourable visual outcome in the long-term.[9,16]

In anterior uveitis, the inflammation breaks down the blood aqueous barrier causing flare, protein leakage, in the anterior chamber. Flare can be measured with a laser flare photometry or by grading based on visual cues on biomicroscopy.[17,74] In a laser flare photometry study by Tappeiner *et al.*, higher flare values correlated with higher anterior chamber cell grades. In their study, higher occurrence of uveitis-related complications was associated with higher flare values at baseline visit but not with anterior chamber cell counts. This finding suggests that flare may express JIA-uveitis-related inflammatory activity separately from anterior chamber cells.[74]

JIA-uveitis is traditionally treated following a stepladder guideline. The first step is glucocorticoid treatment for up to 3 months, after which antirheumatic therapy is introduced if the uveitis is not under control. The second step is methotrexate or another non-biologic DMARD if methotrexate

is not suitable. If uveitis is not under control after 3 months of non-biologic DMARD therapy with or without glucocorticoids, TNF inhibitor treatment is started.[15]

A combination therapy of methotrexate, glucocorticoids and, ideally, TNF inhibitors should be started at the time of diagnosis in patients who have sight-threatening complications and severe ocular inflammation.[14,18]

It should be noted that no studies have been conducted to confirm the best order of the steps – or the duration of each step – in the current treatment guidelines for JIA-uveitis.

2.4.1. GLUCOCORTICOIDS

Treatment for JIA-uveitis is started with a topical glucocorticoid monotherapy for patients with mild uveitis diagnosed without uveitis-related complications.[18,75][18,74] However, there is very little evidence to support the long-term use of topical glucocorticoids in the treatment of JIA-uveitis.[18]

Prednisolone acetate and dexamethasone are the first line choices for topical glucocorticoid treatment for uveitis. Topical glucocorticoids are given at a frequency that is required based on the severity of the inflammation. If inflammation is under control, topical treatment is tapered step by step aiming for glucocorticoid-free remission.[75] If JIA-uveitis is not under control, new complications arise, or if existing complications worsen during topical glucocorticoid treatment, systemic antirheumatic treatment is introduced.[14,18]

In JIA-uveitis, topical glucocorticoid use should be limited to 3 months according to the 2019 American College of Rheumatology/Arthritis Foundation guideline. Their guideline recommends introduction of antirheumatic treatment and tapering of glucocorticoids if 1-2 daily glucocorticoid drops are needed to control the JIA-uveitis. In other words, if controlling JIA-uveitis requires at least one glucocorticoid eye drop every day, the patient should be treated with antirheumatics.[18] In comparison, an older treatment guideline published in 2012 by Heiligenhaus *et al.* endorsed continued topical treatment of JIA-uveitis with as many as 3 glucocorticoid eye drops per day.[15]

Systemic glucocorticoids can be given to selected patients with severe uveitis as a short-term bridging treatment. Otherwise, topical glucocorticoids and systemic antirheumatic therapy are preferred over systemic glucocorticoids in the treatment of JIA-uveitis.[13,14] Glucocorticoids have also been administered periocularly or intraocularly in some patients although no consensus has been reached on their use in treating JIA-uveitis.[14,18,25,76,77]

Long-term use of glucocorticoids should be avoided due to serious side effects, particularly in children.[18,75] Minimising the use of topical glucocorticoids is beneficial in protecting the eye from glucocorticoid-related cataract, ocular hypertension, and glaucoma.[78,79] Systemic side effects of glucocorticoid use include adrenal insufficiency, growth suppression, gastrointestinal and hepatic issues, hyperglycemia, hyperlipidemia, hypertension, osteoporosis, fragility related fractures, and infections.[80–82]

The role of glucocorticoids in the treatment of JIA-uveitis has shrunk between the 2012 and 2019 guidelines.[15,18] Glucocorticoid use may well

continue decreasing in the future as studies and clinical experience show that glucocorticoids are associated with higher rates of ocular complications, complication-related surgeries, and worse visual outcome in JIA-uveitis, compared with systemic antirheumatic treatment.[9,12,16] Randomised, controlled studies are needed to better compare the safety and efficacy of glucocorticoids with non-biologic DMARDs, biologic drugs, or a combination thereof in the long-term treatment of JIA-uveitis.

2.4.2. DMARDS

Methotrexate is the gold standard DMARD for JIA-uveitis. In a review of 52 articles, 73% of the children with JIA-uveitis achieved clinical remission of uveitis, or 2 SUN-grades of improvement with methotrexate.[83] If methotrexate is not suitable because of side effects, other DMARDs can be considered in treating JIA-uveitis.[14,15,18,52,84]

Control of JIA-related uveitis can be expected in 62% of patients with azathioprine monotherapy.[84] Mycophenolic acid maintained good control of uveitis at ≤SUN 0.5+ in 73% of patients with JIA-uveitis in a study by Chang *et al.*[52] Cyclosporin A is of limited value as a monotherapy in JIA-uveitis, but can be effective when combined with methotrexate according to Tappeiner *et al.*[54] Leflunomide should not be used as a treatment for JIA-related uveitis because it associates with a 150% higher flare rate and 50% higher need of TNF inhibitor treatment compared with methotrexate.[85]

Short-term gastrointestinal side effects – especially nausea – are common with methotrexate, azathioprine, and mycophenolic acid treatment.[52,83,84] The long-term safety profile of non-biologic DMARD medication is acceptable.[70,86]

2.4.3. TNF INHIBITORS

TNF inhibitors are biologic drugs that are fully human or humanised antibodies that bind specifically to, and neutralise, human TNF.[87] They induce clinical remission in a wide variety of inflammatory diseases, including uveitis.[15,88] It is not known if the effect of TNF inhibition in JIA-uveitis is mediated primarily locally in the eye, systemically, or both. If local TNF inhibition is required for good control of uveitis, the blood-ocular barrier might be a limiting factor as regards intraocular access of TNF inhibitors, unless this barrier is rendered permeable because of the uveitis.[89,90]

Adalimumab and infliximab are the first-line TNF inhibitors in treating JIA-uveitis.[14,15,18] In the treatment of JIA-uveitis, only adalimumab has been studied in randomised and controlled clinical trials.[43,67]

Patients with JIA-uveitis treated with adalimumab experience consistently high uveitis remission rates as high as 62-67%.[67,91] A randomised controlled trial by Ramanan *et al.* compared methotrexate with placebo (30 patients) to a combination of methotrexate and adalimumab in JIA-uveitis for up to 2 years of treatment. Inactive uveitis defined as zero cells in the anterior chamber was observed in 62% of the adalimumab-

treated patients and in 7% of the placebo-treated patients. Treatment failure was observed in 27% in the adalimumab group and 60% in the placebo group. Hence, treatment failure was reduced by 75% with adalimumab. Treatment failure criteria included no improvement of inflammation in SUN-grades when the baseline SUN grade was ≥1+, a two-grade worsening in SUN grades, ≤1 grade of improvement in SUN grades and development of a new ocular complication; and worsening of an existing ocular complication. Additionally, patients treated with methotrexate and adalimumab had longer duration of inactive disease, and they needed less glucocorticoid treatment than the patients on methotrexate and placebo.[67]

Quartier *et al.* studied a group of young patients (age range, 5-20 years) with active JIA-related uveitis (29 patients) or non-JIA-related idiopathic uveitis (2 patients) who were treated with methotrexate and topical glucocorticoids. Their patients were randomised in an adalimumab treatment group and a placebo group for 2 months. Response to treatment was defined as improvement of laser flare photometry values by ≥30% and no worsening in slit-lamp examination. Response rate was 64% (9 of 14) in the adalimumab group and 20% (3 of 15) in the placebo group at 2 months.[43]

In a study by Llorenç *et al.*, certolizumab pegol controlled uveitis unrelated to JIA in 5 of 7 patients.[92] A multicenter study is being conducted to study the effect of certolizumab pegol in JIA.

Etanercept does not seem to control JIA-related uveitis as effectively as adalimumab and infliximab.[93–96] Both relapses of uveitis and first episodes of uveitis have been reported during treatment with etanercept.[94] This lack in efficacy might be explained by observations of Walters *et al.* who reported that patients with JIA treated with etanercept have a paradoxical increase in TNF levels despite clinical improvement of arthritis.[61] In a small (12 patients) randomised, double-masked, placebo-controlled trial, etanercept was no better than placebo in controlling JIA-uveitis.[95] In a study by Reiff *et al.*, treatment with etanercept led to remission in 4 of 18 eyes (22%) of 10 patients within 3 months of treatment of paediatric JIA-related or non-JIA-related uveitis.[93] Tynjälä *et al.* compared etanercept treatment to infliximab in JIA-uveitis. In their study the uveitis improved in 5 of 24 (21%) patients with etanercept whereas in 9 of 21 (43%) patients with infliximab.[96] The comparatively low success rate with infliximab in the study by Tynjälä *et al.* can be explained by the low drug dosing that was used in the study.[68,96,97]

Golimumab controlled JIA-uveitis of all 3 patients in a report by William *et al.*[98] In a study by Palmou-Fontana *et al.*, 2 of 7 patients maintained control of JIA-uveitis on golimumab.[99]

Infliximab-induced clinical remission varies from 20% to 100% in JIA-uveitis. With infliximab, clinical remission is achieved more commonly with higher doses.[68,97]

2.4.3.1. Safety

Tolerability of TNF inhibitor treatment has been acceptable in patients with JIA. Minor side effects at the site of injection, such as pain, erythema, localised rash, minor haemorrhage, or local irritation are commonly seen.[67–69]

A higher risk of infections has been suspected during TNF inhibition. Among patients with JIA-uveitis, there were 10 adverse events per patient-year with adalimumab treatment whereas a placebo group had 6.5 adverse events per patient-year. Respiratory disorders and infections were the most common side effects in the adalimumab-treated group.[67] In a meta-analysis on the treatment of JIA with any TNF inhibitor, no significant differences in infection rates were found among the TNF inhibitor-treated patients compared to those on other therapies (OR 1.13, 95% CI 0.76-1.69, p=0.54).[100]

Patients receiving TNF inhibitors are at increased risk of mycobacterium tuberculosis infections, which is why latent tuberculosis is screened prior to TNF inhibitor treatment in JIA.[101,102] After a negative screening result, very few paediatric patients develop a mycobacterium tuberculosis infection. In a review including 3003 patients with JIA and treated with TNF inhibitors, one patient was diagnosed with a mild pulmonary infection related to mycobacterium tuberculosis.[101] In a prospective cohort study of 167 paediatric patients with a rheumatic disease and treated with TNF inhibition, 3 patients were diagnosed with latent tuberculosis. They received anti-tuberculosis treatment and were given TNF inhibitors thereafter.[102]

A higher risk of optic neuritis during TNF inhibitor treatment has been suspected.[103] The risk may be higher especially for patients with a family history of demyelinating diseases.[104] The overall prognosis of TNF inhibitor-associated optic nerve inflammation seems favourable in adults.[103] No reports on demyelinating diseases in children, JIA, or JIA-uveitis during TNF inhibitor treatment have been published to date.

Long-term safety reports on treating children with a biologic treatment are lacking. However, no increase in overall mortality or cancer mortality coinciding with TNF inhibitor therapy has been found in large cohort studies.[105,106]

2.4.3.2. ADAb formation

Failure of TNF inhibitor treatment can be caused by immunisation against the given TNF inhibitor.[88,107–109] Exposure to any foreign antigen, such as a TNF inhibitor, can initiate an unwanted host immune response. Endocytosis of the TNF inhibitor by antigen-presenting cells may lead to T effector cell proliferation and activation. T cell activation can cause B cell activation and differentiation into ADAb-secreting B cells and memory B cells.

ADAbs that bind to the drug can impair drug efficacy. If ADAbs bind to functionally relevant parts of the TNF inhibitor and negate its function, they are pharmacologically neutralising. Non-neutralising antibodies bind to pharmacologically irrelevant portions of the drug. Binding of ADAbs to the drug will form immune complexes that can reduce treatment efficacy by enhancing further ADAb production and drug clearance, and by reducing the half-life of the drug.[110]

Endocytosis of the TNF inhibitor by antigen-presenting cells may also lead to drug-specific tolerance. If the antigen is internalised from apoptotic cells instead of necrotic cells, the antigen tolerance is maintained better.

Antigen-specific tolerance is promoted by migrating immature dendritic cells that can suppress auto-reactive T effector cells.[111]

Immune complexes that are formed between TNF inhibitors and ADAbs can provoke potentially harmful hypersensitivity to the drug.[110,111] In a study by Ruperto *et al.*, infliximab-related infusion reactions were more common (58%) among patients with JIA and ADAbs than among patients with JIA but no ADAbs (19%). In their study, anaphylactic reactions occurred only among ADAb-positive patients (4 of 20).[112] In contrast, adverse reactions were not associated with ADAbs when JIA was treated with adalimumab.[69,113] The underlying pathology of this discrepancy remains obscure.[110,111]

Anti-adalimumab antibodies seem to be predominantly neutralising ones.[110] In line with this, ADAb development and related low levels of the drug in the serum have been associated with failure of adalimumab treatment in JIA-related and other types of non-infectious uveitis.[114–116] Only 3 JIA-uveitis-related case series on anti-adalimumab antibodies have been published by October 2020 (II).[115,116] Skrabl-Baumgartner *et al.* reported that 9 of 20 (45%) patients with JIA-uveitis treated with adalimumab had ADAbs.[116] Murias *et al.* found ADAbs in all of their 8 patients with JIA-related or non-JIA-related uveitis.[115] In JIA in general, ADAbs are detected in up to 26% of adalimumab-treated patients.[69,117]

Both drug-related factors and patient-related genetic factors seem to influence immunogenicity of TNF inhibitors.[118,119]

Higher doses of a TNF inhibitor might protect patients against formation of ADAbs because serum levels of ADAbs have reversed after increasing dosing of a TNF inhibitor.[111,120] Lower prevalence of ADAbs and higher clinical remission rates have been reported in patients with higher doses of TNF inhibitors.[97,112,121,122] This result is consistent in all studies[97,112,121,122] but that of Aeschlimann *et al.*, in which patients with ADAbs were given a lower dose of infliximab by a mean of 0.2 mg/kg and no association was found between the dosing and ADAb formation in JIA or JIA-uveitis.[123]

Treatment with methotrexate is a known protective factor against formation of ADAbs in JIA and other diseases.[69,107,108,117,124] In a meta-analysis on adalimumab treatment for JIA, concomitant use of methotrexate reduced the risk of ADAb development by 67%.[124] In a meta-analysis by Garcês *et al.*, concomitant methotrexate or azathioprine or mercaptopurine reduced the frequency of ADAb formation during treatment with adalimumab or infliximab by 47% among patients with rheumatoid arthritis, spondylarthropathies, psoriasis, and inflammatory bowel diseases.[107] A higher dose of methotrexate has been associated with lower immunogenicity against adalimumab among patients with rheumatoid arthritis.[125] High levels of a TNF ligand, called B cell activating factor, have been associated with lack of anti-TNF antibody formation in patients and in experimental animal models receiving concomitant methotrexate.[126] Nevertheless, it remains unclear exactly how methotrexate treatment modulates the immunisation against TNF inhibitors. One hypothesis is that because methotrexate can reduce the overall level of inflammation and TNF production, fewer TNF inhibitor molecules get consumed, which may result in higher TNF inhibitor trough levels and lower ADAb formation.[119] If lowering the overall inflammatory level impacts ADAb formation, other DMARDs should also protect against ADAbs. However, among non-biologic DMARDs, only

methotrexate, azathioprine, and mercaptopurine seem to protect against ADAb formation.[69,107,108,117,119,124] Moreover, the ADAb-reducing effect of azathioprine is found only in patients with Crohn's disease.[119]

Unfortunately, therapeutic serum levels for any medication needed for successful treatment of JIA-uveitis are presently unknown. Furthermore, some patients seem to maintain sufficient disease control despite forming ADAbs, at least in rheumatoid arthritis, spondylarthropaties, inflammatory bowel diseases, and psoriasis.[107] The current clinical practice is to give the patient a higher dose of the TNF inhibitor, methotrexate, or both, to prevent treatment failure if the patient has a low trough level of TNF inhibitor with or without ADAbs, a poor control of inflammation, or both. If increasing doses does not improve the efficacy of the treatment, another biologic drug is chosen.[107,108,124]

Immunisation against another TNF inhibitor is common after development of ADAbs against one TNF inhibitor although ADAbs are drug-specific. This may be explained by potentially predisposing genetic variations.[118] When switching TNF inhibitors, special care should be taken in dosing methotrexate and TNF inhibitor to prevent ADAb development.[107,120] If TNF inhibitor treatment fails, tocilizumab or rituximab can be considered as alternative therapies in JIA-uveitis.[53,56(p),58,127,128]

2.4.4. OTHER BIOLOGIC TREATMENTS

Abatacept is a T cell co-stimulation modulator that inhibits T cell activation. In a multicenter setting, 21 patients with active JIA-uveitis were given abatacept. Three (14%) patients sustained inactivity of uveitis until their uveitis recurred after tapering of glucocorticoids and DMARDs.[55] In another study, 35 patients with JIA-uveitis were given abatacept either as a first-line biologic drug or a second-line drug after treatment failure with TNF inhibitors. Seventeen patients had remission of uveitis with abatacept treatment. A clinical remission rate of 55% was achieved after excluding 4 patients who discontinued their treatment.[57]

Rituximab is a monoclonal antibody directed against a B cell marker. Although uveitis seems to be a T cell-mediated disease, rituximab induced inactivity of JIA-uveitis in 7 of 10 patients within 6-9 months. Uveitis recurred in 3 of 7 patients and retreatment with rituximab re-induced their uveitis inactivity.[127]

Tocilizumab is an anti-interleukin-6 receptor antibody. IL-6 is a proinflammatory cytokine that induces proliferation and differentiation of T cells and differentiation of B cells**.** Increased IL-6 serum levels have been found in patients with uveitis and other inflammatory diseases.[129] In a study by Tappeiner *et al.*, tocilizumab was given to 17 patients with JIA-uveitis, whereafter 10 (59%) of them achieved inactive uveitis. Additionally, uveitis-related macular oedema resolved in 5 patients with tocilizumab.[58] In another case report, 9 of 13 (69%) patients achieved remission of uveitis with tocilizumab.[128]

2.5. OCULAR COMPLICATIONS

Ocular complications eventually occur in the majority of eyes with JIA-uveitis.[8,9,12,13,16,130,131] Ocular complications are especially common in eyes with uveitis diagnosis close to the onset of arthritis highlighting the importance of early uveitis screening in JIA.[41] In newly diagnosed JIA-uveitis, complications are found in 21-67% of eyes.[4,8,19,132] Ocular complications are associated with reduced visual acuity and blindness in JIA-uveitis.[8,9,13,19]

Common JIA-uveitis-related complications include band keratopathy, posterior synechiae, cataract, low IOP, high IOP and related secondary glaucoma, and macular oedema (Table 4). Less common complications include epiretinal membrane formation, retinal vasculitis, retinal detachment, and optic disc oedema.[8,9,13,19,133,134]

Table 4. Ocular complications in JIA-uveitis

Complication	Angeles-Han *et al.*[13]	Gregory *et al.*[9]	Kump *et al.*[133]	Rypdal *et al.*[41]
Band keratopathy	25 %	36 %	46 %	7 %
Posterior synechiae	31 %	30 %	58 %	14 %
Cataract	31 %	N/A	64 %	24 %
Glaucoma, elevated IOP	17 %	16 %	20 %	22 %
Macular oedema	15 %	12 %	N/A %	7 %

Advanced band keratopathy, cataract, and macular oedema cause direct obscuration of the central vision. They are among the most common complications that cause poor vision in JIA-uveitis.[19] Posterior synechiae are associated with poor visual prognosis also, although they generally do not have any direct impact on vision.[8,19] Glaucoma causes optic nerve damage and permanent visual field loss that can eventually be absolute so that the eye loses the ability to perceive light.[82,130,131] Ocular hypotony (IOP <5 mmHg) occurs in 3-18% of eyes with JIA-uveitis.[9,41,135] Ocular hypotony is associated with severe loss of vision in eyes with uveitis. Risk factors for ocular hypotony include prior glaucoma surgery, cataract surgery, and pars plana vitrectomy. Ocular hypotony is often an untreatable condition. Chronic ocular hypotony can lead to loss of function and shrinking of the eye – phthisis bulbi – which is an end-stage for the eye.[135]

Active inflammation, high-grade uveitis, and diagnosis of uveitis at first visit are associated with higher complication rates in JIA-uveitis.[8,13,16,19] Further complications can develop during treatment and follow-up. Thorne *et al*. reported that new complications occurred at a rate of 0.33 per eye-year during a 3 year follow-up.[16] Further complications develop more frequently in eyes that have pre-existing JIA-uveitis-related complications.[9] Higher level of inflammation measured by laser flare photometry associates with more frequent ocular complications.[136] Glucocorticoid treatment increases the incidence of complications. Local and systemic glucocorticoids show a dose-dependent association with both cataract formation and high

IOP.[78,79,137] Antirheumatic immunosuppressive treatment reduces the risk of several complications, including cataract,[79] low IOP,[16] high IOP,[82] epiretinal membrane formation,[16] and macular oedema.[138(p)] Moreover, low visual acuity from JIA-uveitis is less common in patients treated with antirheumatics than in those without antirheumatic treatment.[9,16]

2.5.1. CATARACT

Up to 64% of patients with JIA-uveitis develop a cataract at a young age.[13,133] Cataract surgery is performed at a mean time of 3.3-4.5 years after the diagnosis of JIA-uveitis, at around 11 years of age.[29,139,140]

Risk of developing a cataract in JIA-uveitis is associated with posterior synechiae, active uveitis, and use of glucocorticoids.[79,140] Thorne *et al.* reported that patients treated with ≤3 glucocorticoid eye drops daily had an 87% lower risk of having a cataract than patients treated with >3 drops.[79] This is why a 2012 guideline for managing JIA-uveitis suggests that topical glucocorticoid treatment is kept at a maximum 3 drops per day.[15] A 2019 guideline does not recommend using corticosteroid eye drops as frequently as once per day in the long-term.[18]

Methotrexate may lower the risk of cataract development and delay the need for cataract surgery by a mean of 3.5 years.[140]

2.5.1.1. Cataract surgery

Postoperative course and visual prognosis after cataract surgery are generally worse in JIA-uveitis than in uveitis related to other diseases.[32] BenEzra and Cohen published in 2000 that BCVA ≥0.5 was achieved only in 2 of 9 eyes with JIA-uveitis after cataract surgery with or without primary IOL implantation.[141]

Later studies have shown more favourable results in cataract surgery with primary IOL implantation in JIA-uveitis.[29,30,139] In a retrospective study by Grajewski *et al.* in 2012, the mean BCVA was 0.5 in decimal notation (logMAR 0.3, SD 0.2) after a mean of 2.2 years of follow-up.[30] In 2006, Kotaniemi and Penttilä from Finland reported a rate of 64% for BCVA ≥0.5 after a mean of 3.3 years of follow-up.[29] In 2019, Kulik *et al.* confirmed a similar rate of 65% for BCVA ≥0.5 after 34 cataract surgeries in 24 patients. Their median follow-up was 10.9 years (range, 1.0-23.1). Further comparison can not be made with the current or previous studies because follow-up details were available for only 17 of 24 patients and not for individual eyes.[139]

Postoperative complications are common after cataract surgery of eyes with JIA-uveitis. Unfortunately, complication rates in eyes with JIA-uveitis but without cataract surgery are not available for comparison. Cataract surgery-related complications include new synechiae, persistent inflammation, pupillary membranes, fibrinoid reactions, IOP rise and secondary glaucoma, ocular hypotony and related phthisis bulbi, IOL decentration, IOL deposits and pigmentation, PCO and retrolental membrane formation, and chronic macular oedema.[28–30,141,142]

Secondary glaucoma is a common complication of JIA-uveitis with or without cataract surgery. Both Kotaniemi *et al.*[29] and Kulik *et al.*[139] studied JIA-uveitis-related cataract surgeries with or without posterior capsulotomy and anterior vitrectomy. They found that secondary glaucoma was present in 38-39% of eyes prior to cataract surgery. Secondary glaucoma developed in 19-38% of previously unaffected eyes. By the end of the follow-up, frequency of secondary glaucoma was 50-62% and frequency of glaucoma surgery was 39-53%.[29,139] Considering the overall complication rates in JIA-uveitis, glaucoma may be more common in eyes after cataract surgery (50-62%)[29,139] than in eyes with or without cataract surgery (14-42%).[20,82,131,143]

Macular oedema has been detected in 14-44% of eyes with JIA-uveitis after cataract extraction and primary IOL implantation,[29,139] which suggests that the rate of macular oedema is at least as common after cataract surgery as compared with overall frequencies of macular oedema (3-48%) in JIA-uveitis with or without cataract surgery.[13,19,26,144]

More rarely reported complications of cataract surgery in JIA-uveitis include postoperative corneal decompensation (6%), [139] retinal detachment (6%),[29] and severe ocular hypotony resulting in phthisis (6%).[139]

2.5.1.2. Primary intraocular lens implantation

Primary intraocular lens implantation has been a topic of controversy in cataract surgery of JIA-uveitis.[142]

In 2010, Sijssens *et al.* reported that long-term visual outcome was better in pseudophakic than aphakic eyes after cataract surgery in JIA-uveitis until 7 years. In their study, complication rates of macular oedema, optic disc oedema, ocular hypertension, glaucoma, and ocular hypotony did not differ between the pseudophakic and aphakic group.[145] On the contrary, Magli *et al.* reported a higher incidence of secondary glaucoma after primary compared with secondary IOL implantation in patients with JIA-uveitis.[31]

In Helsinki University Hospital, primary IOL implantation has been a preferred practice over secondary implantation or aphakia in JIA-uveitis since the 1990's. All eyes structurally suitable for a primary in-the-bag IOL have been implanted with an IOL, although some experts suggest that patients with persisting hypotony or active uveitis should be left aphakic at cataract surgery.[29,141]

No publications compare different IOL options in JIA-uveitis-related cataract surgery. In a review and meta-analysis of cataract surgery in various types of uveitis, eyes receiving an acrylic or a heparin-surface-modified PMMA IOL achieved better visual acuity outcomes than eyes receiving a non-heparin-surface-modified PMMA or a silicone IOL.[146] With regard to uveitis reactivation and PCO development, hydrophilic and hydrophobic lenses seem to perform equally well in eyes with uveitis.[147,148] A hydrophobic acrylic IOL has been the primary choice in JIA-uveitis-related cataract surgery in Helsinki University Hospital.

2.5.1.3. Anterior vitrectomy in cataract surgery

Anterior vitrectomy and primary posterior capsulotomy have been thought to reduce the incidence of postoperative PCO in paediatric cataract surgery.[149] In children, PCO develops in 41-100% of eyes with uveitis with or without JIA.[29,30,139,150,151] In addition to PCO, fibroelastic retrolental membranes at the level of the posterior capsule can develop in pseudophakic eyes.[150,151] Retrolental membrane development might be less common in patients treated with antirheumatic medication, and when anterior vitrectomy with posterior capsulotomy is performed during cataract surgery.[30] Postsurgical PCO and retrolental membranes can be removed with an Nd:YAG laser, or surgically.[29,30,139,141,150]

Posterior capsulotomy with anterior vitrectomy is traditionally performed during cataract surgery in eyes with paediatric uveitis, with or without JIA, because it is thought to reduce both PCO and retrolental membrane formation.[31,141,145,150] In contrast, some studies have shown that PCO and retrolental membranes develop in eyes with uveitis despite a posterior capsulotomy and anterior vitrectomy.[29,139,141,150] In Helsinki University Hospital and some other centers, auxiliary posterior capsulotomy and anterior vitrectomy during cataract surgery is currently reserved for very young patients in hopes of delaying the need for postoperative removal of any opacification, and for eyes with vitreous pathology.[139,150]

2.5.1.4. Controlling the inflammation during cataract surgery

Eyes with JIA-uveitis are thought to have a tendency to develop a more severe inflammatory response to cataract surgery than eyes with other types of childhood-onset uveitis.[28,32,141] Quiñones *et al.* found that most patients with a postsurgical relapse of uveitis were patients with JIA. In their series, most patients with JIA were left aphakic and had a more severe course of uveitis also preoperatively. No multivariable analysis was carried out to identify other possible variables contributing to postoperative relapses.[32] On the contrary, Grajewski *et al.* reported that their patients with JIA-uveitis did not have any relapses after cataract surgery with IOL implantation.[30]

Perioperative intravitreal triamcinolone injection may reduce postoperative flare-ups and fibrin formation in JIA-uveitis.[30,152] In a retrospective chart review of 22 patients with JIA-uveitis undergoing lensectomy and anterior vitrectomy, 12 patients were given a 4 mg injection of intraocular triamcinolone, and 10 patients were given systemic intravenous and oral glucocorticoids. No fibrin reaction occurred in the triamcinolone group whereas 5 of 10 patients in the systemic glucocorticoid group had postoperative fibrin formation.[152] In one center, 8 eyes with JIA-uveitis received a sustained-release dexamethasone implant during cataract surgery. Two eyes developed a postoperative flare-up despite the implant. This result should be considered anecdotal because of the small study size and lack of a control group.[153]

In a review and meta-analysis of cataract surgeries in various types of uveitis, better preoperative control of uveitis was associated with better outcomes.[146] Also in JIA-uveitis, antirheumatic therapy and meticulous

control of uveal inflammation may lead to improved outcomes after cataract extraction.[31,32] Unrelated to cataract surgery, antirheumatic treatment and better control of uveitis prevent and treat ocular complications, and improve the visual outcome in JIA-uveitis.[9,12,16,29,32,139] Moreover, eyes with less co-pathology have better chances for attaining favourable outcomes after cataract surgery in general.[154] All these findings are interconnected and it is unclear if the recent improvement in results following cataract surgery in JIA-uveitis results from overall healthier eyes undergoing cataract surgery, more careful control of uveitis, giving patients antirheumatic treatment during cataract surgery, or a combination of them.

At present, a safe practice in JIA-uveitis is to perform cataract surgery only in eyes with remission or ≤SUN 0.5+ uveitis, control their inflammation meticulously, and use antirheumatic treatment before, during, and after cataract surgery.

2.5.2. SECONDARY GLAUCOMA

Glaucoma is a major risk factor for severe vision loss in JIA-uveitis.[9,20,82,131,137,143] Glaucoma develops in 14-42% of eyes with JIA-uveitis.[20,82,131,143] In children, the diagnosis of glaucoma is based on elevated IOP and detected optic nerve rim loss because reliable visual fields can be hard to obtain. The optic disc damage and visual field loss may develop quickly and they are irreversible.[82,130,131]

Elevated IOP is very common in JIA-uveitis. In a follow-up study of 196 eyes with JIA-uveitis, 61% had ocular hypertension or secondary glaucoma.[82] IOP starts to rise most often during the first 2 to 3 years after diagnosis of paediatric uveitis with or without JIA.[82,155] In JIA-uveitis, the risk of developing glaucoma continues to increase beyond 7 years from diagnosis.[156] Among patients with JIA-uveitis, the risk of elevated IOP is higher if uveitis is active (> SUN 1+) and if topical or systemic glucocorticoids are used, whereas the risk is lower with systemic antirheumatic treatment.[82,137] Severe vision loss ≤0.1 is almost four times as common with high IOP than without high IOP in JIA-uveitis.[82]

The pathogenesis of uveitis-related IOP-elevation and glaucoma is undetermined.[157] It is likely that inflammatory cells, proteins and debris obstruct the trabecular meshwork and constrain the aqueous humour outflow in eyes with chronic uveitis. Proinflammatory cytokines, enzymes, and free radicals have been studied but a direct causation has not been found between them and IOP-elevation in uveitis.[157]

Glucocorticoid treatment – which is common in uveitis – is a well-known risk factor for high IOP and glaucoma.[82] The pathogenesis of glucocorticoid-induced glaucoma is unknown.[157] In a multicenter study on 916 children with any non-infectious uveitis, the risk of elevated IOP increased with topical glucocorticoids in a dose-response manner.[78] In their multivariate analysis, HR for IOP ≥21 mmHg was 0.75 (95% CI, 0.28-2.03, $p<0.001$) with 1 glucocorticoid drop, 3.06 (95% CI, 1.67-5.60, $p<0.001$) with 2 drops, 3.57 (95% CI, 1.82-7.02, $p<0.001$) with 3 drops, and 4.61 (95% CI, 2.81-7.57, $p<0.001$) with 4 glucocorticoid drops per day compared with no topical glucocorticoid treatment. With glucocorticoid injections, HR for IOP ≥21

mmHg was 7.96 (95% CI, 4.29-14.7, $p<0.001$) for periocular and 6.96 (95% CI, 1.41-34.2, $p=0.02$) for intraocular ones compared with no glucocorticoid injections. Systemic prednisolone ≤7.5 mg and >7.5 mg had an association with high IOP in an univariable analysis ($p=0.01$ and $p=0.02$, respectively).[78]

Based on these studies,[9,20,78,82,131,137,143] experts suggest that patients with JIA-uveitis are given antirheumatics instead of 1-3 glucocorticoid drops per day in the long-term to reduce the risk of elevating IOP. Furthermore, if IOP is elevated, glucocorticoid treatment should be replaced by antirheumatics,[18] because high IOP associates with severe vision loss in JIA-uveitis.[9,20,82,131,137,143]

2.5.2.1. Topical treatment

Topical IOP-lowering medication is the first-line therapy for elevated IOP. The majority of patients with JIA-uveitis with high IOP require at least 2 topical medications to control their IOP.[82] However, very few studies report the efficacy and safety of antiglaucomatous medication in children. Beta-blockers, carbonic anhydrase inhibitors and prostaglandin analogs seem effective and well tolerated in children. Alpha-2-agonists have potentially serious adverse effects in young children and should not be used in paediatric patients. Often the first choice for antiglaucomatous medication for paediatric patients is timolol that can be combined with carbonic anhydrase inhibitors for an improved IOP-lowering effect. Prostaglandin analogs might be less effective in reducing IOP in children than in adults.[158] Antiglaucomatous medication provides sufficient control of IOP in only 26-32% of eyes with elevated IOP in JIA-uveitis.[82,143]

2.5.2.2. Surgical treatment

Surgical treatment is required in up to 62% of the eyes with JIA-uveitis to control high IOP and to prevent secondary glaucoma-related optic nerve damage.[20,82,143] Neither comparative studies nor a commonly accepted treatment of choice exist for the surgical care of JIA-uveitis-related high IOP.

The IOP-lowering procedures performed in JIA-uveitis include trabeculectomy,[11,21,159] deep sclerectomy,[21,160] glaucoma drainage devices,[23,161] goniosurgery,[22] and transscleral diode cyclophotocoagulation.[162] Surgical success is usually defined as IOP ≤21 mmHg without further IOP-lowering operations and without IOP-lowering medication. In general, prior ocular surgery, young age, and uveitis are known risk factors for surgical failure in glaucoma surgery.[163] Hence the success rate of glaucoma surgery in JIA-uveitis is low, and a mean of 2.6 surgeries are required to control high IOP of JIA-uveitis. In comparison, adult eyes with uveitis require a mean of 1.6 IOP-lowering operations to gain sufficient IOP control.[143]

2.5.2.3. Trabeculectomy with or without MMC

Trabeculectomy is a common surgical choice for JIA-uveitis-related glaucoma.[11,21,164] In trabeculectomy, a piece of trabecular meshwork is removed under a scleral flap to increase the outflow of aqueous humour from the eye through the flap. The outgoing aqueous humour forms a filtering bleb under the conjunctiva and is slowly absorbed to conjunctival vessels. Increased outflow of aqueous humour decreases the IOP.[165]

In adult eyes without uveitis, trabeculectomies can have successful survival rates with IOP ≤21 mmHg that are as high as 57% at 20 years without additional antiglaucomatous medication, and 88% with such medication.[166] In JIA-uveitis, trabeculectomy success rates have been lower.[11,21] A study by de Boer *et al.* included 9 trabeculectomies performed in eyes with JIA-uveitis. Five of 9 surgeries were successful in controlling the IOP.[11] Heinz *et al.* reported 12 trabeculectomies in JIA-uveitis. One survived without medication, 8 survived with medication, and 3 trabeculectomies failed to control IOP ≤21 mmHg despite IOP-lowering medication.[21] In paediatric uveitis not specifically associated with JIA, success rate of trabeculectomy has been 55% during 61 months (SD, 26) with or without antiglaucomatous medication.[159]

Postoperative scarring of the filtering bleb and subsequent occlusion of the filtration cause failure to maintain IOP ≤21 mmHg after filtration surgery. In general, children have a more active postoperative fibrotic response and scar formation than adults.[164,167] Accordingly, young age at the time of surgery is a known risk factor for filtration failure.[166] Other risk factors for filtration failure are prior intraocular surgery[163] and uveitis.[166] Among patients with paediatric uveitis, JIA has been associated with a lower surgical success rate after filtration surgery.[21] In summary, paediatric patients with JIA-uveitis who undergo a trabeculectomy have a poor prognosis of maintaining IOP ≤21 mmHg.

Surgical outcome after filtration surgery can be improved by using antimetabolites such as MMC,[164] a chemotherapeutic drug that inhibits DNA, RNA and protein synthesis. MMC is applied to the trabeculectomy site to reduce postoperative fibrinogenesis and scarring of the filtration bleb in uveitis-related and other glaucoma surgery.[160,163,164] The safety of MMC augmentation has been a topic of controversy because higher rates of postoperative endophthalmitis have been suspected after MMC use in paediatric glaucoma surgery.[164] According to a Cochrane Database Systematic Review, MMC seems to reduce the relative risk of trabeculectomy failure. Following treatment with MMC, cataract formation might be more common but no significant increase in any other side effect, including infections, seem to exist in eyes with trabeculectomies.[168] MMC-augmentation is a standard practice in trabeculectomies in Helsinki University Hospital.

TNF is a cytokine that plays a role in promoting scar formation through angiogenesis and collagen synthesis.[169] It has been shown to enhance the proliferation of fibroblasts of human Tenon's capsule.[170] Elevated TNF levels in the aqueous humour – a common occurrence in uveitis – has been associated with filtration failure.[171] Topical treatment with TNF inhibitors has been shown to suppress postoperative ocular scarring in experimental

animal models.[172,173] Therefore, adding TNF inhibitor treatment to MMC-augmented trabeculectomies is an attractive treatment option for improving filtration success of trabeculectomies in uveitis eyes.

In JIA-uveitis, trabeculectomy-related postoperative complications include cataract development, ocular hypotony and hypotony-related shallow anterior chamber, macular oedema, and choroidal detachment.[21] Other less common trabeculectomy-related complications not specific to JIA-uveitis are bleb leakage, anterior chamber haemorrhage, infection of the bleb, and purulent endophthalmitis.[165,166] The available patient series are too small to reliably estimate any frequencies for trabeculectomy-related complications in JIA-uveitis.[11,21] In a patient series on adult uveitis-related glaucoma, cataract progression occurred in 45% and ocular hypotony in 30% of eyes that had undergone trabeculectomy.[174] Saeedi *et al.* reported that ocular hypotony-related macular oedema following trabeculectomy is more common in secondary glaucoma, such as uveitis-related glaucoma, than in primary glaucoma.[175] Also, ocular hypotony-related macular oedema following trabeculectomy is more common in paediatric patients than in adult ones.[175] At the same time, prolonged ocular hypotony tends to be rare in children, which likely results from their more brisk healing response.[159]

Despite the complications mentioned, BCVA may not decrease after trabeculectomy in JIA-uveitis.[21]

2.5.2.4. Deep sclerectomy

Deep sclerectomy is a form of non-penetrating filtration surgery that might not be as effective as trabeculectomy in controlling IOP of patients with paediatric uveitis. In a study by Heinz *et al.*, failure to control IOP occurred during the first postoperative year in 4 of 8 deep sclerectomies compared with 2 of 16 trabeculectomies.[21] To date, no studies are available that report on deep sclerectomy in JIA-uveitis-related secondary glaucoma. In adult uveitis-related glaucoma, success rates of deep sclerectomy are 69% at best in controlling the IOP ≤21 mmHg up to 5 years.[176]

2.5.2.5. Glaucoma drainage device

Glaucoma drainage devices create a secondary pathway for the aqueous humour outflow. A tube-shunt is inserted in the anterior chamber and a bleb-forming endplate is set in the subconjunctival space.[177] In a study by Välimäki *et al.*, a drainage device implantation was performed in 27 eyes with JIA-uveitis. Ninety percent of the eyes retained an IOP ≤21 mmHg with or without antiglaucomatous medication until 52 months. Postoperative complications occurred after 14 (52%) surgeries, and 15% of the eyes lost at least 1 line of vision during follow-up.[23] Eksioglu *et al.* studied a group of patients with paediatric uveitis and secondary glaucoma after implantation of a drainage device with a valve. The cumulative probability of success without antiglaucomatous medication was 42% at 48 months and 25% at 84 months, and the cumulative probability of complications was 51% at 48 months and 75% at 108 months.[161]

2.5.2.6. Goniosurgery

There are no publications on goniosurgery performed specifically in JIA-related uveitis in the literature by October 2020. In paediatric uveitis-related glaucoma, 48-55% of goniosurgeries survive 2-234 months.[22,178] Transient hyphaemas are seen in 80% of the eyes undergoing goniosurgery. Cataract extraction is required in 28% of the eyes after goniosurgery. Better surgical outcome has been found among patients without prior intraocular surgery, patients younger than 10 years of age at surgery, and patients with fewer anterior synechiae.[22]

2.5.2.7. Transscleral diode cyclophotocoagulation

According to Heinz *et al.*, transscleral diode cyclophotocoagulation does not provide satisfactory control of high IOP in JIA-uveitis-related glaucoma. In their study, 19 eyes were treated 41 times with transscleral diode cyclophotocoagulation. The IOP remained ≤21 mmHg in 6 of 19 eyes (32%) with IOP-lowering medication during 10 months (SD, 9).[162]

2.5.3. MACULAR OEDEMA

Macular oedema is the most common cause of visual impairment in chronic uveitis.[2] Macular thickening and cystoid oedema occur in 3-48% of patients with JIA-uveitis.[13,19,26,144]

In a study by Ducos de Lahitte *et al.*, macular changes were detected in 84% of 61 eyes (38 patients) with JIA-uveitis. Only four eyes had no changes in their OCT scan. Macular oedema was found in 48%, foveal serous retinal detachment in 18%, perifoveal thickening without macular oedema or without a foveal serous detachment in 22%, and atrophic changes were found in 10% of the studied eyes. Visual impairment associated with foveal thickening in OCT.[144] The same research group later discovered that resolution of a foveal serous retinal detachment associates with improvement in visual acuity and reduced anterior chamber flare.[179]

In a study by de Boer *et al.*, 21% (13 of 61) of patients with JIA-uveitis had macular oedema. In their series, macula oedema was associated with decreased vision and longer disease duration, but not with higher SUN grades.[26] Angeles-Han *et al.* reported that 15% (8 of 52) of patients with JIA-uveitis had a history of cystoid macular oedema. In their study, cystoid macular oedema was associated with vision loss.[13]

No drug of choice to treat macular oedema in JIA-uveitis or other types of non-infectious uveitis is available. Intraocular and systemic glucocorticoids and antirheumatic drugs have all been used[1,14,15,18,25,26,76,138,179–182] but to date, no comparative studies regarding the different treatment options when treating JIA-uveitis-related macular oedema have been published.

2.5.3.1. Biologic treatment

Macular thickening and oedema have been shown to resolve during biologic antirheumatic treatment.[53,56,138,180] In a study by García-de-Vicuña *et al.*, adalimumab reduced macular thickness from 305 μm (SD, 125) to 231 μm (SD, 31) during 6 months in 39 patients with JIA-uveitis.[180] In a study by Calvo-Río *et al.*, a reduction in central macular thickness and oedema from a mean of 463 μm (SD, 124) to 254 μm (SD, 30) was measured in 9 patients with JIA-uveitis receiving adalimumab for 6 months. Another 17 patients had macular thickening without cystoid oedema. Their mean macular thickness decreased from 371 μm (SD, 134) to 249 μm (SD, 28) with a 6-month treatment with adalimumab.[138]

In a study by Calvo-Río *et al.*, tocilizumab reduced macular thickness from 402 μm to 259 μm in 9 patients with treatment-resistant JIA-uveitis and cystoid macular oedema.[56] In a study by Tappeiner *et al.*, tocilizumab resolved JIA-uveitis-related macular oedema in 5 eyes.[53]

Abatacept has reportedly resolved JIA-uveitis-related macular oedema in one patient.[183]

2.5.3.2. Systemic glucocorticoid treatment

Systemic glucocorticoid treatment can help in achieving rapid recovery of macular oedema in uveitis.[184] It can be prescribed at a dose of 0.5-1 mg/kg per day in JIA-uveitis to treat macular oedema, but not all patients respond sufficiently to systemic glucocorticoid treatment.[27] Long-term use of systemic glucocorticoids is not advisable in children, considering the systemic side effects.[80,185]

2.5.3.3. Intravitreal triamcinolone

In a retrospective series of paediatric uveitis by Sallam *et al.*, not specifically in patients with JIA, intravitreal triamcinolone resolved macular oedema in 16 children. The oedema relapsed in 31% of the eyes within 7 months. Complications were common after intravitreal triamcinolone treatment with IOP rise in 31% and cataract progression in 55% of the eyes.[25] No available reports on intravitreal triamcinolone in the treatment of JIA-uveitis-related macular oedema have been published by October 2020.

2.5.3.4. Sustained-release intravitreal dexamethasone implant

Sustained-release intravitreal glucocorticoid implants have been recommended when antirheumatic therapy fails to resolve macular oedema in uveitis.[1]

Pichi *et al.* injected a sustained-release dexamethasone implant in 17 eyes with JIA-uveitis. Nine eyes had related macular oedema. The mean central retinal thickness reduced from 438 μm (SD, 96) to 342 μm (SD, 79) with one injection. After the first injection, 5 of 9 eyes continued to have macular oedema and they were given a second injection. After the second injection,

mean central retinal thickness improved in 4 of 5 eyes from 400 μm (SD, 60) to 250 μm (SD, 14), and one eye continued to have macular oedema. Repeated injections were needed at a mean interval of 7-7.5 months to control the relapses.[77] Among the 17 eyes with dexamethasone implants, mean IOP increased from 15 mmHg to 25 mmHg at 1 month and was 23 mmHg at 3 months. Cataract progression happened in 8 of 12 (66%) phakic eyes treated with dexamethasone implants with or without macular oedema. As a result, cataract surgery was required in 3 eyes.[77]

Sella *et al.* inserted intravitreal dexamethasone implants in 14 eyes with paediatric intermediate or posterior uveitis, non-specific to JIA. Macular oedema decreased in all of them. Visual acuity improved in 12 of 14 eyes. Because of relapses in macular oedema after 3-6 months, 5 eyes were retreated. Three patients showed cataract progression and two had an elevated IOP during the study.[76]

In conclusion, an intravitreal dexamethasone implant seems to decrease macular oedema in JIA-uveitis for a limited period of time in many patients but repeated injections are often required and complications may occur.[76,77]

2.5.3.5. Sustained-release FAI

Retisert® (Bausch & Lomb, Rochester, New York, USA) is a non-biodegradable vehicle for a pellet containing 0.59 mg of fluocinolone acetonide, a synthetic glucocorticoid. A tablet is made of fluocinolone acetonide and inactive microcrystalline cellulose, magnesium stearate, and polyvinyl alcohol. The tablet is set on top of a polyvinyl alcohol membrane in a silicone elastomer cup. The resulting implant is 3 x 2 x 5 mm in size. It is implanted through a pars plana sclerotomy and secured with sutures in the sclera. It is designed to release fluocinolone acetonide at a steady rate during 30 to 36 months. After implantation, fluocinolone acetonide is found in similar concentrations in the iris, ciliary body, retina, and lens.[186]

The 0.59 mg FAI has been effective in resolving macular oedema associated with intermediate uveitis, posterior uveitis, and panuveitis in adults. In adult eyes with uveitis, FAI has provided long-lasting glucocorticoid release and control of inflammation at least until 54 months, according to the Multicenter Uveitis Steroid Treatment Trial. FAI-treated eyes had faster resolution of macular oedema than eyes with systemic antirheumatic treatment until 6 months of follow-up, whereafter no significant difference was found between the two groups. The Multicenter Uveitis Steroid Treatment Trial did not enroll patients with macular oedema related to anterior JIA-uveitis, and direct inference cannot be drawn from their results to treatment of JIA-uveitis.[182] Ocular complications are far more common in eyes treated with FAIs than in eyes treated with systemic antirheumatic treatment.[182] Complications are also more common after 0.59 mg FAIs than after shorter lasting dexamethasone implants.[76,77,187–189] After 0.59 mg FAI insertion, cataract surgery is required in all phakic eyes.[187,189] IOP rise is seen in 65% of eyes, and IOP-lowering surgery is required in 32% eyes.[188] The Retisert® implant is no longer commercially available.

Fluocinolone acetonide implants are available as non-biodegradable tubes containing 0.18-0.19 mg of fluocinolone acetonide. The FAI tubes are

inserted in the vitreous through pars plana with a 25-gauge needle. In a randomised and controlled trial, 129 eyes with recurrent non-infectious posterior uveitis were treated with a sham injection or an FAI containing 0.18 mg of fluocinolone acetonide. Mean central macular thickness decreased by 61 μm in the FAI treatment group and increased by 8 μm in the sham group during 12 months. Among phakic eyes, cataract extraction was required in 33% after FAI treatment and 12% after sham treatment during the first 12 months of the study. Mean IOP rise was 1.3 mmHg (SD, 3.6) in the FAI and 0.2 (SD, 4.2) in the sham treatment group.[190] So far, 0.18-0.19 mg FAIs have not been studied in JIA-uveitis-related macular oedema. They might provide an alternative intravitreal method for treating uveitis-related macular oedema in the future.

3. AIMS OF THE PRESENT STUDY

The overall aim of the present study was to identify possible positive and negative prognostic factors related to the treatment of JIA-uveitis and its complications. Its specific aims were to:

1. Study the effect of TNF inhibitor treatment on survival of MMC-augmented trabeculectomy in JIA-uveitis (I)
2. Evaluate the association of anti-adalimumab antibody formation with treatment failure in JIA-uveitis (II)
3. Find a therapeutic adalimumab trough level for JIA-uveitis (II)
4. Chart the resolution of chronic macular oedema after FAI implantation in JIA-uveitis (III)
5. Report the long-term results of cataract surgery with primary IOL implantation in JIA-uveitis (IV)
6. Evaluate prognostic factors for maintaining good BCVA after cataract surgery in JIA-uveitis (IV)

4. PATIENTS AND METHODS

Eligible to the study were patients with JIA-uveitis who had undergone an MMC-augmented trabeculectomy in April 1996 to January 2014 (I), were treated with adalimumab in 2014-2016 (II), had undergone an FAI implantation in 2010-2012 (III), or a cataract surgery from February 2000 to April 2012 (IV) in the Department of Ophthalmology, Helsinki University Hospital, Helsinki, Finland. All studies were retrospective observational case series.

Studies I and III included one eye of each patient. In study IV, both eyes were included in the analysis if the patient had undergone cataract surgery in both eyes. In study II, remission of uveitis was defined as 0 cells in the anterior chamber in both eyes and in case of active uveitis, only the eye with higher SUN grade was included in the statistical analysis. The studied groups in I-IV were interrelated (Table 5). By chance and because of the long study period, no patient was enrolled in more than 2 studies I-IV. The total number of studied patients was 70.

Table 5. Interrelationships of the studies I-IV

	Trabeculectomy	ADAbs	FAI	Cataract	Total
Trabeculectomy (I)	29			9	
ADAbs (II)		31	1	4	
FAI (III)			8	2	
Cataract (IV)				26	
Total number of eyes					78

Paediatric rheumatologists set the diagnosis of JIA using ILAR criteria.[39] Ophthalmologists screened all patients with JIA for uveitis at the Department of Ophthalmology. Onset of uveitis was coded as the date of diagnosis by an ophthalmologist. Uveitis was graded using SUN criteria.[17] Antirheumatic medication was chosen in coordination with paediatric rheumatologists to achieve remission of arthritis and either remission or no more than mild SUN 0.5+ grade of uveitis. Despite all efforts, some patients did not reach this target and they were given maximum tolerated medication to maintain the lowest possible level of inflammation (I-IV).

IOP was measured with Goldman applanation tonometer, when applicable, or the Icare TA01i rebound tonometer (Icare Finland Oy, Vantaa, Finland). For older patients, BCVA was recorded in decimal notation with a Rodenstock chart monitor (Rodenstock Instruments, Nürnberg, Germany). BCVA in younger patients was recorded with a Lea symbol® chart (Good-Lite, Elgin Illinois, USA). BCVA <0.05 was converted to decimal notation following Lange et al.[191] Heidelberg OCT (Heidelberg SPECTRALIS®, Heidelberg Engineering, Germany) imaging was performed at every visit for

detecting macular oedema in the FAI study (III), and in studies I and IV only if macular oedema was suspected clinically.

4.1. MAIN OUTCOME MEASURES

The different main outcome measures were IOP ≤21 mmHg in the trabeculectomy study (I), ADAbs and degree of inflammation in the anti-adalimumab antibody study (II), macular oedema in the FAI study (III), and BCVA in the cataract study (IV). (Table 6)

4.2. SECONDARY OUTCOME MEASURES

Overlapping secondary outcome measures were IOP (III,IV), uveitis activity (I,III,IV), BCVA (I,III), macular oedema (I,IV), and cataract formation (I,III). IOP, uveitis activity, BCVA, and macular oedema were also overlapping with primary outcome measures (Table 6).

Nine eyes of 9 patients from the trabeculectomy study (I) were also enrolled in the cataract analysis (IV). Six eyes undergoing cataract extraction (IV) had undergone a prior MMC-trabeculectomy (I). Five trabeculectomies survived after cataract extraction. One eye had a failing trabeculectomy and required a tube-shunt implantation after cataract extraction. Three eyes without a prior glaucoma diagnosis required an MMC-trabeculectomy after their cataract operation and were enrolled in the trabeculectomy study (I). There was no overlap between the trabeculectomy follow-up (I) and the start of the ADAb study (II). There was no overlap between the trabeculectomy (I) and FAI series (III). (Table 5)

BCVA was a primary outcome measure in the cataract study (IV) and a secondary outcome measure in the FAI study (III). Two eyes of two patients were included in both studies (III,IV). One eye underwent cataract extraction prior to FAI implantation. Another eye underwent FAI surgery for chronic macular oedema, and a cataract extraction 6 months thereafter. (Table 5)

The anti-adalimumab antibody study (II) overlapped with the FAI study (III) by 1 patient and the cataract study (IV) by 4 patients. (Table 5)

Table 6. Interrelationships of the primary and secondary outcomes

	Outcome measure			
Study	**IOP**	**Visual acuity**	**Macular oedema**	**Uveitis activity**
Trabeculectomy (I)	primary	secondary	secondary	secondary
ADAbs (II)	–	–	–	primary
FAI (III)	secondary	secondary	primary	secondary
Cataract (IV)	secondary	primary	secondary	secondary

4.3. MMC-TRABECULECTOMY

Fifty-five consecutive primary MMC-augmented trabeculectomies were performed for 30 patients with JIA-uveitis in April 1996 to January 2014. The surgical indication was glaucomatous optic nerve damage and failure to control IOP at ≤21 mmHg with maximal tolerated IOP-lowering medication. Fifteen patients were treated with TNF inhibitors, whereas 14 patients did not receive them at the time of the surgery. To avoid confounding factors, one patient was excluded from the study because they were treated with a biologic drug, abatacept, but not with a TNF inhibitor. Prior trabeculectomy was an exclusion criterion, whereas eyes with any other intraocular surgery were allowed.

The purpose of this retrospective analysis was to compare the surgical success of patients treated with TNF inhibitors and without them at the time of the surgery. For the analysis, one eye was drawn at random from each of the 14 patients that had undergone a bilateral MMC-trabeculectomy. Twenty-nine eyes were studied further in the analysis. By chance, all eyes with prior ocular surgery got drawn to the study.

4.4. ANTI-ADALIMUMAB ANTIBODIES

The inclusion criteria for the study were age of ≤16 years and treatment of JIA-related uveitis with adalimumab for ≥6 months in Helsinki University Hospital during 2014-2016. Thirty-one patients were enrolled in the study. For the statistical analysis, the eye with higher-grade of uveitis was chosen in case of bilateral uveitis.

In Helsinki University Hospital, patients with JIA-uveitis and inadequate response to adalimumab are monitored for ADAbs as needed. Patients with adequate response to adalimumab were screened for adalimumab trough levels and anti-adalimumab antibodies routinely every 1 to 2 years in 2014 to 2016. The blood samples were drawn a maximum of 24 hours before the next scheduled adalimumab administration. The samples were analysed in United Medix Laboratories, Helsinki, Finland. Enzyme immunoassays were used for trough level measurements and radioimmunoassays for ADAb measurements.

4.5. FAI IMPLANTATION

Eight eyes of 8 patients with JIA-uveitis who were treated with a 0.59 mg FAI for treatment-resistant macular oedema were enrolled in the analysis. Nine patients were FAI-treated during 2010-2012 in Helsinki University Hospital. One patient was excluded from the study because they dropped out after the first follow-up visit.

4.6. CATARACT SURGERY

Twenty-six consecutive cataract surgeries with primary IOL implantation were performed for 20 patients <20 years of age with JIA-uveitis-related cataract. Posterior capsulotomy and anterior vitrectomy were performed only for patients with vitreous pathology or <4 years of age at surgery. Five of 26 eyes required a posterior capsulotomy and anterior vitrectomy. Intraoperative intravitreal glucocorticoid injections were not given. There was no standard of practice in preoperative and postoperative care for eyes with JIA-uveitis undergoing cataract surgery in 2000 to 2012.

4.7. STATISTICAL METHODS

For statistical analysis, SPSS (version 19; IBM, New York, USA) and Stata (version 13 and 15, Stata Corp, College Station, Texas, USA) were used. Both SPSS and Stata were used for the statistical analysis of the trabeculectomy study (I). The anti-adalimumab study (II) and cataract study (IV) were executed with Stata. SPSS was used in the FAI study (III). All tests were two-sided and $p<0.05$ was considered significant.

A mean was calculated for normally distributed variables. A median and range was calculated for other variables. The 95% CI was calculated for main findings, when applicable.

Unordered and singly-ordered categorical variables were compared with Fisher's exact and Kruskal-Wallis test, respectively (I,II,IV). Continuous variables were compared with Mann-Whitney *U* independent samples test (II). Spearman's rank correlation was used when comparing continuous variables against activity of uveitis in SUN grades, and preoperative SUN grades against postoperative ones (II,IV). Nonparametric test for trend was used when comparing continuous variables between ordered groups, such as SUN grades, and presence or absence of methotrexate or ADAbs.[192] Wilcoxon signed-rank test was used for comparing pre- and postoperative IOP (IV). Kaplan-Meier survival analysis with a log-rank test, stratified by subgroups, were performed to analyse variables contributing to survival (I,IV).[193] Prognostic factors (independent variables) of ADAb formation >12 AU/ml (dependent variable) were examined by multiple logistic regression analysis (II).

5. RESULTS

5.1. MMC-TRABECULECTOMY

At five years, the only difference detected between the failing and surviving group of trabeculectomies was TNF inhibitor treatment at the time of surgery (p=0.020, Fisher's exact test). In Kaplan-Meier analysis, the cumulative proportion of eyes with IOP ≤21 mmHg was 73% (95% CI, 44-89) at 1, 5 and 10 years for patients on TNF inhibitor treatment during surgery, whereas for patients without TNF inhibition, success rate decreased from 57% (95% CI, 28-78) at 1 year to 0% by 10 years (p=0.007, log-rank test) (I, Figure in I).

Potential additional predictors influencing the survival were modeled stratifying the analysis by subgroups. The effect of TNF inhibition persisted in subgroups of JIA (oligoarthritis or polyarthritis), history of prior surgery (yes or no), surgeon, age of the patient (tertiles; <9, 9-12.9, and ≥13 years) and duration of uveitis (tertiles; <4, 4-7.9, and ≥8 years) at trabeculectomy. No differences were detected between the patients with or without TNF inhibition at surgery when comparing the age at diagnosis of uveitis or JIA, duration of uveitis, age at glaucoma surgery, use of DMARDs at the time of surgery, preoperative IOP or SUN grade, prior ocular surgery, postoperative complications, postoperative SUN grade, or BCVA at the last follow-up. TNF inhibition at the time of the surgery remained the only variable identified that was associated with longer survival of MMC-augmented trabeculectomy in JIA-uveitis (I).

Postoperative ocular hypotony was measured in 17 of 29 eyes (59%). Ocular hypotony related maculopathy was observed in 10 eyes (34%). Hypotony and related maculopathy resolved within 48 days (median, 14) in all affected eyes. No association was detected between TNF inhibitor treatment at surgery and ocular hypotony (p=0.68, Fisher's exact test) or TNF inhibitor treatment and duration of ocular hypotony (p=0.42, Mann-Whitney U test). Other observed postoperative complications were hyphaema (2 eyes), bleb hemorrhage (1), shallow anterior chamber (7), and choroidal detachment (2). The median postoperative BCVA was 0.9 (range, 0.005-1.1) (I).

5.2. ANTI-ADALIMUMAB ANTIBODIES

Remission of uveitis was maintained in 15 of 31 patients (48%), 9 (29%) had mild SUN 0.5+ uveitis and 7 (23%) had a higher-grade uveitis at least in one eye during adalimumab treatment with or without methotrexate. Remission of uveitis was found only among patients without ADAb formation (p=0.001, Fisher's exact test). An association was found between ADAb formation and lack of methotrexate treatment (p=0.043, Fisher's exact test). Other prognostic factors for ADAb development were younger age at diagnosis of JIA or uveitis (p=0.046 and p=0.030, logistic regression

analysis, respectively). No adalimumab-related serious adverse effects occurred during the study period (II).

ADAb formation-related low or undetectable adalimumab trough levels were detected in 9 of 31 (29%) patients. Among these 9 patients, SUN 0.5+ uveitis was found in 4, a more active uveitis in 4, and 1 patient relapsed from mild to higher-grade uveitis after discontinuation of adalimumab. Higher-grade uveitis was associated with ADAb formation, although 2 patients had active uveitis without detectable ADAbs ($p<0.001$, nonparametric test for trend) (II).

Among the 22 patients with no measurable ADAb formation, the median adalimumab trough level was 9.4 mg/l (range, 4.0-24.0). Higher adalimumab trough levels were associated with higher adalimumab doses ($p=0.0032$, Spearman's correlation). Methotrexate treatment or lack thereof was not associated with adalimumab trough levels ($p=0.23$, Mann-Whitney *U* test). Methotrexate dose was not associated with adalimumab trough levels ($p=0.89$, Spearman's correlation). Higher adalimumab trough levels were not associated with better control of uveitis ($p=0.86$, nonparametric test for trend). Thus, the results do not suggest a therapeutic trough level for adalimumab in the treatment of JIA-uveitis (II).

5.3. FAI IMPLANTATION

Each of the 8 patients had a complete resolution of macular oedema in 2-20 weeks after the FAI surgery. The preoperative median BCVA was 0.08. Postoperative median BCVA improved to 0.5 at 1, 2 and 3 years, 0.63 at 4 years, and 0.7 at 5 years after the FAI surgery. Two eyes maintained a low BCVA ≤0.16 despite complete resolution of macular oedema. Three relapses were detected at 2.7-5.5 years after the FAI surgery. The relapses were treated with antirheumatic medication in two and with a dexamethasone implant in one eye (III).

Postoperative complications were common. All four phakic eyes needed cataract extraction after FAI implantation. Six of 8 eyes had IOP rise >21 mmHg, and 4 required IOP-lowering surgery for IOP ≥30 mmHg. One retinal detachment developed after FAI surgery that was combined with an epiretinal membrane peeling during vitrectomy (III).

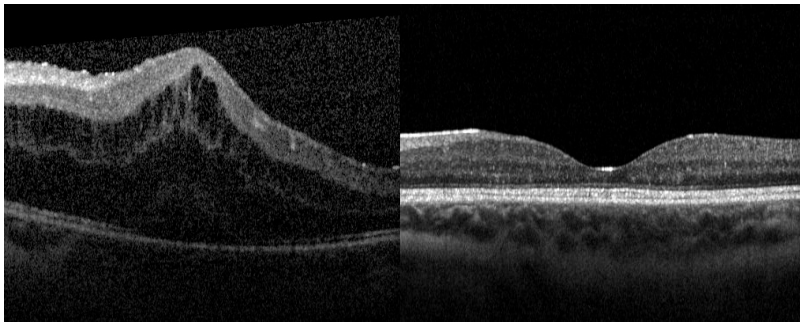

Figure 1. OCT images of an eye prior to the fluocinolone acetonide implant (BCVA 0.05) and at 5.6 years postoperatively (BCVA 0.4)

5.4. CATARACT SURGERY

Median postoperative BCVA was 1.0 in 26 eyes at 5 years and 0.9 in 13 eyes at 10 years of follow-up (IV). Two eyes did not gain BCVA ≥0.5 with the surgery and 2 eyes lost that level of vision during the follow-up. Active uveitis during 3 and 12 months preoperatively was the only risk factor detected for low BCVA <0.5 (p=0.005 and p=0.007, nonparametric test for trend, respectively) (IV).

Preoperative uveitis activity ranged from remission to SUN 4+ (median, SUN 0.5+). Eyes that had more active uveitis preoperatively continued to have more active uveitis also postoperatively (p=0.029 during 3 months and p=0.014 during 12 months postoperatively, Spearman's correlation) (IV).

The median IOP was 13 mmHg preoperatively and 15 mmHg on the first postoperative day (p=0.54, Wilcoxon signed-rank test). Postoperative ocular hypotony was observed in one previously unaffected eye and one previously affected eye. Both of them had undergone a posterior capsulotomy with anterior vitrectomy during cataract extraction (IV).

Frequency of secondary glaucoma was 62% prior to cataract surgery and 73% during the 5 to 10 years of follow-up. Ten eyes underwent glaucoma surgery prior to the cataract surgery, and 4 of them required additional IOP-lowering surgery after the cataract surgery. Additional 3 previously unaffected eyes developed glaucoma and required IOP-lowering surgery 5.8 to 13.6 years after the cataract surgery (IV).

PCO or retrolental membrane at the level of the posterior capsule was detected in 23 of 26 (88%) eyes during the follow-up. Treatment of the secondary opacification was required in 18 eyes, and repeated treatment was required in 4 eyes. Repeated treatment of a secondary opacification was performed only in eyes that had not undergone a primary posterior capsulotomy and anterior vitrectomy (IV).

No new cases of synechiae, pupillary membranes, vitreous haze and cells, or macular oedema were detected. Despite the lack of intraoperative triamcinolone injections, no postoperative fibrinoid reactions developed. (IV).

6. DISCUSSION

JIA-uveitis is a rare disease although it is more common in the Nordic countries than elsewhere.[4,6,41] JIA-uveitis-related ocular complications and surgeries are even more rare than the disease itself, which is why the patient series are small in JIA-specific uveitis research regarding ocular complications.

Some research groups report on variable case mixes of different types of paediatric uveitis. Because the nature of uveitis can vary depending on the intraocular tissues involved and the associated disease, results regarding uveitis that is not specific to JIA cannot be extended directly to JIA-uveitis to formulate treatment guidelines. For this reason, the present research was limited to JIA-uveitis alone. Because JIA-uveitis has a tendency to lead to multiple ocular complications in one eye, non-overlapping patient series regarding the treatment of complications were not achievable, despite the two decade long study period from 1996 to 2018. In essence, this study is a convenience sample, and therefore subject to sampling error and lack of representation of the population.

In studying JIA-uveitis, it is challenging to maintain a standardised treatment protocol because of the relapsing nature and individual, diverse course of the arthritis and uveitis. Therefore, most JIA-uveitis studies are retrospective chart reviews, small case series, or case reports. Even prospective studies in JIA-uveitis are often observational because the treatment has to be personalised.[43]

In this study, observational study design was chosen to make allowance to the relapsing nature of JIA and uveitis although such a retrospective and uncontrolled study design is subject to bias. Prospective study design was not an option for JIA-uveitis-related glaucoma (I), macular oedema (III) and cataract (IV) -related studies because the frequency of those complications, luckily, has decreased after adapting an antirheumatic focused treatment protocol and sparing glucocorticoid treatment.[79,82,138,140,180] That said, studies I, III and IV would have benefitted from a more standardised pre- and postoperative antirheumatic and glucocorticoid treatment regimen at the time of the surgery. Treatment with adalimumab followed a standardised protocol for JIA-uveitis in Helsinki University Hospital during the study period, which was helpful when analysing the patient data in 2016 (II). Adalimumab treatment is common in JIA-uveitis and therefore the anti-adalimumab antibody study could have been designed as a prospective study (II). Yet, randomisation of adalimumab-treated patients to study groups with or without methotrexate would not have been ethically acceptable, given the benefits of concomitant methotrexate during TNF inhibition.[111,117,123,194,195] Therefore, a retrospective study design was adopted also for the anti-adalimumab antibody study (II).

The rarity and relapsing nature of JIA-uveitis introduce limitations to acquiring firm scientific data on the treatment of JIA-uveitis and its complications. The scarcity of controlled data results in controversies, diverse treatment protocols, and lack of generally agreed treatment

guidelines. Bigger patient series through collaboration, prospective and controlled study protocols, longer follow-ups, and limiting the studies to paediatric patients with JIA-uveitis would benefit the field of JIA-uveitis-related research.

6.1. MMC-TRABECULECTOMY

The first MMC-augmented trabeculectomies during TNF inhibitor therapy for JIA-uveitis were performed in Helsinki University Hospital in 2001 and 2003. Curiously enough, the IOP of patients with TNF inhibition during surgery remained ≤21 mmHg for years, whereas MMC-trabeculectomies without TNF inhibition performed during 2001-2003 failed within the first postoperative year (I).

In other trabeculectomy studies related to JIA-uveitis, 8 of 12 and 6 of 9 eyes (both, 66%) retained IOP ≤21 mmHg with or without additional antiglaucomatous medication after surgery.[11,21] In my study, survival was defined as IOP ≤21 mmHg without additional IOP-lowering medication or surgery. Despite the stricter survival criterion compared to earlier studies,[11,21] the survival rate of my study was higher, 73% (I).

A difference in trabeculectomy survival rates with and without TNF inhibition was 57 percentage points at 5 years and 73 percentage points at 10 years after surgery, which suggests that TNF inhibition protects patients against scarring of the trabeculectomy site and subsequent filtration failure (I). Earlier experimental models support the interpretation that TNF inhibitors have a desired influence on wound healing after trabeculectomy.[172,173] No other meaningful variables influencing survival were found among the patients that were enrolled in my trabeculectomy study (I).

Two patients, who were not given TNF inhibitors during the trabeculectomy but were put on TNF inhibition ≥1 year after the trabeculectomy, had failing trabeculectomies during TNF inhibition (I). It seems that, similarly as with mitomycin C treatment, TNF inhibition is required already during surgery to get the wound healing benefits.[163,168,174] It is unclear for how long TNF inhibition should continue before and after surgery to protect against filtration failure.[173]

A study on topical TNF inhibition during trabeculectomy is an interesting prospect for future.[173] On the other hand, potential risk for ADAb formation exists when TNF inhibitor levels are low, which limits the experimental use of topical TNF inhibitors. The level of risk of ADAb formation when using topical TNF inhibition is currently not known.[121,122]

Focus should be shifted from the best practice of IOP-lowering surgery to efforts to prevent IOP-elevation because it associates with a high risk of losing vision in JIA-uveitis.[82] Glucocorticoid treatment is a significant risk factor for IOP-elevation in JIA-uveitis, whereas antirheumatic treatment reduces the risk of IOP-elevation.[78,82] Encouragingly, clinical practice with a glucocorticoid-spearing treatment protocol has reduced the frequency of secondary glaucoma and related IOP-lowering surgeries in these young

patients with JIA-uveitis in Finland and Scandinavia (unpublished observations).

6.2. ANTI-ADALIMUMAB ANTIBODIES

In clinical practice and in earlier studies, JIA-uveitis remains active or relapses in roughly one third of adalimumab-treated patients despite treatment.[67,91] Furthermore, ADAbs have been found in 11-37% of JIA patients,[69,117,195] and ADAb formation has been associated with treatment failure in a plethora of diseases, including JIA.[69,107,109,113,114,117,124,195,196] No reports were previously available on the association between anti-adalimumab antibodies and treatment failure in JIA-uveitis, which is why I designed a retrospective study on this topic in Helsinki University Hospital in 2016. In my study, ADAb formation was associated with a failure to achieve remission and a higher-grade uveitis among adalimumab-treated patients with JIA-uveitis (II).

In a review and meta-analysis by Doeleman *et al.* on ADAb formation in JIA, 6 adalimumab-related original studies published in PubMed, Embase, and Cochrane Library published by July 2018 met their inclusion criteria.[124] One of them was my study (II). The studies covered 323 patients with JIA with or without uveitis. The pooled prevalence of anti-adalimumab antibodies was 22% (95% CI, 14-30). Lower ADAb prevalence rates were found in series with shorter follow-ups (48-60 weeks), whereas in my study with a median follow-up of 3.1 years, ADAb rate was as high as 29% (II).[124] Although higher ADAb rates could be partially explained with a longer follow-up time in the meta-analysis,[124] duration of adalimumab treatment was not a risk factor for ADAb formation in my study (II).

In daily clinical practice, the key questions are: how can we recognise the patients who are at high risk of ADAb-related treatment failure and how can we prevent treatment failure.

Treatment with methotrexate is associated with a lower risk of anti-adalimumab formation among patients with JIA with or without uveitis. Among patients with JIA and treated with adalimumab, the risk ratio of developing ADAbs with concomitant methotrexate is 0.33 compared to patients without methotrexate (95% CI, 0.21-0.52, $p<0.01$).[124] An association between lower methotrexate dose and more frequent ADAb formation has been reported in studies on adult-onset autoimmune diseases.[119] This association does not exist among patients with JIA, which can be possibly explained by how problematic it is to track drug dosing accurately according to body weight or body surface in growing children in long follow-up settings (II).

Not all relapses during TNF inhibition can be explained by ADAb formation (II).[124] Clinical experience shows that patient compliance and unnecessary breaks from the treatment coincide with some of the relapses. But even with good compliance, two patients in my patient series did not achieve good control of uveitis despite the lack of measurable ADAbs and trough levels ≥7.0 mg/ml (II). Furthermore, Burgos-Vargas *et al.*[196(p)] and

Lovell *et al.*[113] found no clinically significant association between ADAb formation and JIA-treatment failure.

Transient ADAbs could be one explanation for treatment failure without measurable ADAbs.[116,195] Detecting transient ADAbs requires repeated blood samples, which is neither a cost-effective nor patient-friendly clinical practice. Clinical experience shows that increasing the TNF inhibitor dose is a sensible practice in JIA-uveitis when patients with or without measurable ADAbs lose treatment effect.[18] Switching biologic agents is the last option because there are only two biologic drugs that are repeatedly shown to be effective in JIA-uveitis.[18] In other autoimmune diseases that can be treated effectively with multiple different biologic drugs, switching biologic agents can possibly be done more freely.[124]

It has been suggested that ADAb reversal can be achieved by increasing TNF inhibitor dosing.[111,120] In my study, one patient with an adalimumab trough level of 4.0 mg/l, ADAb level of 19 AU/ml and mild uveitis was given adalimumab with a shorter interval after which their ADAbs remained undetectable. Clinical remission of uveitis was achieved with an adalimumab trough level of 8.4 mg/ml (II). Bigger and prospective patient series would be beneficial in analysing the association between higher adalimumab dosing and lack of ADAbs suggested in the smaller retrospective case series.[111,120]

More clinical research is needed to provide us with comprehensive tools to prevent treatment failures and uveitis flare-ups from happening during TNF inhibitor treatment. Variables that should be studied further include genetic predisposition, lapses in the medication including compliance issues, changes in the inflammatory activity, and growth of the patient resulting in a need for higher antirheumatic drug dosing.

Until we know more about ADAb formation and TNF inhibitor-related treatment failure, it is good practice to keep adalimumab-treated patients on an adequate adalimumab dose, continuous treatment regimen, and concomitant methotrexate, whenever applicable, to reduce the risk of ADAbs and related treatment failure.

6.3. FAI IMPLANTATION

Earlier studies show that antirheumatic treatment is slower acting but as effective as a sustained-release 0.59 mg FAI in treating macular oedema of intermediate, posterior, and panuveitis in adults.[182] No study reported on intravitreal sustained-release FAIs in JIA-uveitis until FAI treatments were started in Helsinki University Hospital. In my study, FAI surgery was a last-resort treatment for 8 patients with treatment-resistant chronic macular oedema related to JIA-uveitis. Prior systemic glucocorticoid treatment, antirheumatic therapy, and intravitreal short-acting glucocorticoids had not resolved their macular oedema (III).

Close monitoring after FAI surgery is needed because of its high postoperative complication rate.[182,187,188] Cataract surgery is required in all phakic eyes after implanting an 0.59 mg FAI (III).[187] A 10 mmHg increase in IOP or increase to IOP ≥30 mmHg is reported in 65% of 0.59 mg FAI-treated eyes with posterior uveitis.[188] Also in my study, 4 of 8 eyes had IOP ≥30

mmHg requiring IOP-lowering surgery, and additional 3 eyes had their IOP increase by 10 mmHg (III).

After the last FAI treatment for JIA-uveitis in Helsinki University Hospital (III), intravitreal dexamethasone implants were shown to reduce macular oedema in the short term in JIA-uveitis and paediatric uveitis. 0.59 mg FAIs seem to provide longer lasting control of macular oedema than dexamethasone implants. Repeated dexamethasone implant injections are needed to control the relapses, starting as early as 3 months after the first one,[76,77] whereas relapses occurred as late as 2.7-5.5 years after FAI surgery in my study (III).

From 2012, research groups have been reporting on the positive effect of adalimumab and tocilizumab on macular oedema in JIA-uveitis.[53,56,138,180] Reviewing the patient charts, none of the FAI-treated patients were treated with tocilizumab or with the highest recommended doses of adalimumab or infliximab[18] prior the FAI surgeries in 2010-2012 (III). Three patients from the FAI study had a relapsing macular oedema and were successfully treated with antirheumatics (2) and an intravitreal dexamethasone implant (1 patient) (III). More recently, three paediatric patients with uveitis and related macular oedema have been treated with high-dose TNF inhibitors to resolve their macular oedema. No intravitreal glucocorticoid treatment or long-term systemic glucocorticoid treatment have been required for any of them (unpublished data).

My results suggest that if antirheumatic medication combined with systemic glucocorticoid treatment fails to resolve chronic macular oedema in JIA-uveitis, FAI surgery should be considered, carefully balancing the high complication rate with the potential benefits associated with FAI surgeries (III). As the 0.59 mg FAIs are no longer available, we will have to wait and see if the 0.18-0.19 mg FAIs provide similar control of macular oedema in JIA-uveitis as the higher-dose FAI.

As we are changing our treatment guidelines towards a protocol that is more antirheumatic treatment centred, macular oedema might become a less common feature in JIA-uveitis. In the event of JIA-uveitis-related macular oedema, treatment with biologics[53,56,138,180] should be favored over intravitreal glucocorticoid treatment in young patients considering ocular complications and intraocular surgeries associated with intravitreal glucocorticoid treatment (III).[77,182,187,188]

6.4. CATARACT SURGERY

In my study with a minimum of 5 years of follow-up, 77% of the eyes retained BCVA 0.5 or higher (IV). It provides the lowest reported rate of BCVA <0.5 (4 of 26 eyes) after cataract surgery in JIA-uveitis.[29–31,139] In a study from Finland by Kotaniemi and Penttilä published in 2006, 64% of the eyes obtained BCVA 0.5 after a mean of 3.3 years (SD, 3.2) of follow-up.[29] In a study by Kulik *et al.* published in 2019, 65% of the eyes retained a BCVA ≥0.5 for a median of 10.9 years (range, 1.0-23.1). Unfortunately, the earlier reports did not include results at 5 and 10-year cut-off points or a Kaplan-Meier estimate to allow easier comparison with my study.

In my study, worse BCVA was associated with higher preoperative uveitis activity (IV). This association between higher uveitis activity and worse visual prognosis is also seen in earlier reports.[31,32] Low uveitis activity and antirheumatic treatment are known favourable prognostic factors in JIA-uveitis in general.[3,9] More common antirheumatic treatment and low uveitis activity at the time of the surgery may explain the improved BCVA results in the more current studies (IV) [139] compared with earlier studies.[29–31,141] In my study, 7 of 26 (27%) eyes had active uveitis >SUN 0.5+ during 3 months preoperatively (IV). Unfortunately, other authors have not reported preoperative uveitis activity in a standard form as cells /1 mm^2, or perioperative medications which is why further comparisons cannot be made with my study results (IV).[29–31,139]

No standardised protocol is in place for pre- and postoperative care with antirheumatic and glucocorticoid treatment in JIA-uveitis-related cataract surgery. In my patient series, topical glucocorticoids were adjusted according to the uveitis activity both pre- and postoperatively. Unfortunately, the frequencies of topical treatment were not routinely recorded in the patient database. Four patients undergoing 6 cataract extractions had a discontinuation in their antirheumatic treatment either 1-2 weeks before, 1-3 weeks after, or both, during their cataract surgery. In turn, four patients undergoing 5 cataract surgeries were given systemic prednisolone during the surgery. Their inflammatory activity varied from SUN 0 to SUN 1+. With this varying degree of pre- and postoperative medication, the eyes that had low-grade uveitis preoperatively continued to have lower-grade uveitis postoperatively, and eyes with high-grade uveitis continued to have higher-grade uveitis also postoperatively (IV). A prospective study design with a standardised protocol for pre- and postoperative medication is needed to better understand the impact of uveitis activity and antirheumatic medication on surgical results of cataract extraction in JIA-uveitis.

Li *et al.* compared patients with JIA-uveitis undergoing cataract surgery with or without an auxiliary intravitreal triamcinolone injection.[152] Five of 10 patients without intravitreal triamcinolone developed postoperative fibrin formation, whereas no fibrin formation occurred among 12 patients with intravitreal triamcinolone. Their results indicate that triamcinolone should be used during cataract surgery.[152] Conversely, postoperative fibrin formation did not occur in my study, despite the patients were not given intravitreal glucocorticoids during cataract surgery. My results suggest that a perioperative intravitreal glucocorticoid injection to prevent fibrin formation after cataract extraction is not mandatory in eyes with well-controlled JIA-uveitis (IV). However, both the study by Li *et al.* and my study are limited by a small study sample and retrospective nature (IV).[152] Larger studies are needed to clarify the role of intravitreal glucocorticoids in cataract surgery of JIA-uveitis.

In my study, PCO was a common postoperative complication in eyes with and without a primary posterior capsulotomy and anterior vitrectomy during cataract surgery. The subgroup of patients not needing treatment for PCO and the subgroup of eyes with posterior capsulotomy and anterior vitrectomy were too small to study them further (IV). Also previous results on the impact of anterior vitrectomy and posterior capsulotomy on PCO and retrolental membrane formation in eyes with uveitis are inconclusive because

some studies have shown that PCO and retrolental membranes tend to develop despite a primary posterior capsulotomy and anterior vitrectomy.[29,139,141,150]

When discussing postsurgical complications such as ocular hypotony, high IOP and related glaucoma, and macular oedema, it is important to note that JIA-uveitis has a high complication rate in and by itself,[4,8,19,132] and further JIA-uveitis related complications are more common in eyes with previous complications.[16] Hence, it is questionable if especially late-onset complications are related only to the previously performed surgery.

Prior to the cataract surgeries, 16 of 26 eyes in my series were affected by secondary glaucoma and 3 additional eyes developed glaucoma thereafter (IV). By the end of follow-up, the frequency of secondary glaucoma in my study was 73%. Kulik *et al.* had diagnosed secondary glaucoma in 38% of eyes prior to cataract surgery, and glaucoma developed in 24% of eyes after surgery, resulting in a 62% rate of secondary glaucoma at the last visit.[139] In my study, IOP-lowering surgery was required in 38% of the eyes 0.2-13.6 years after cataract surgery (IV), compared to 53% in the study by Kulik *et al.*[139] Thus, secondary glaucoma seems to be a common complication before cataract surgery in eyes with JIA-uveitis-related cataract and even more common after surgery (IV).[29,139] My study design that omitted a control group does not allow further analysis of possible variables influencing the frequency of glaucoma after JIA-uveitis-related cataract surgery (IV).

Ocular hypotony occurs in 5-18% of eyes with JIA-uveitis.[9,135] Known risk factors for ocular hypotony include cataract surgery, glaucoma surgery, and pars plana vitrectomy.[135] In my cataract surgery series, four eyes underwent an anterior vitrectomy during cataract surgery and a glaucoma surgery prior or after cataract surgery. Another 12 eyes underwent a prior or later glaucoma surgery. Despite the potential high risk for ocular hypotony after cataract surgery among my patients, only one previously unaffected eye developed ocular hypotony. The eye retained a BCVA 0.8 during 9 years of follow-up. Another eye had chronic ocular hypotony and related vision loss already prior the surgery (IV). Also Kulik *et al.* reported that 2 eyes (6%) had severe ocular hypotony after cataract surgery, resulting in phthisis bulbi and vision loss.[139]

In earlier reports, 15-44% of eyes with JIA-uveitis have been diagnosed with macular oedema after cataract surgery.[29,139] In my study, macular oedema was not recorded routinely with an OCT but only when oedema was suspected clinically. Only two eyes (8%) were diagnosed with macular oedema after cataract surgery. The rate of macular oedema might have been higher had OCT imaging been performed for all eyes after cataract surgery (IV).

In JIA-uveitis-related cataract treatment, focus should be shifted from the best practice of cataract surgery to efforts to prevent or delay cataract formation and the need for cataract surgery in these young patients. Glucocorticoid treatment is a known risk factor for cataract development in JIA-uveitis,[79] which is one of the reasons why the 2019 American College of Rheumatology guideline[18(p)] suggests fewer than 1 to 2 glucocorticoid eye drops per day in the treatment of JIA-uveitis in contrast to the 2012 guideline[15] that endorsed using 3 daily drops of glucocorticoids. Glucocorticoid-sparing treatment means more focus on DMARDs and

biologic drugs. Moreover, methotrexate has already been associated with a lower risk of cataract formation and with delaying cataract surgery.[140] Clinical practice with an antirheumatic therapy-focused treatment of JIA-uveitis and a simultaneously decreasing cataract surgery rate together with previous study results encourages uveitis specialists and paediatric rheumatologists to focus on glucocorticoid-sparing treatment in young patients with JIA-uveitis.

7. RECOMMENDATIONS

7.1. MMC- TRABECULECTOMY

In JIA-uveitis in general, it is advisable to consider avoiding glucocorticoid treatment whenever possible and to treat patients primarily with antirheumatic medication to avoid secondary IOP problems.[28,78,82] In recent years, the need for IOP-lowering surgeries has decreased among patients with JIA-uveitis treated in Finland after adapting a more active approach with antirheumatic treatment and a reduction in glucocorticoid therapy (unpublished observations). This clinical impression is in line with previous studies on the protective factors and risk factors of high IOP and secondary glaucoma in JIA-uveitis.[82,137]

If IOP-lowering surgery is required in JIA-uveitis; the current research is not extensive enough to give a recommendation on the type of surgery that should be chosen (I).[11,21–23] My study suggests that if MMC-augmented trabeculectomy is required, TNF inhibition should not be discontinued preoperatively (I). Experimental short-term use of TNF inhibition for its wound-healing benefits cannot be recommended.[67,86,124] In general, TNF inhibitor treatment should be considered for all patients with secondary glaucoma related to JIA-uveitis that is not well-controlled.[14,28,67]

7.2. ANTI-ADALIMUMAB ANTIBODIES

Treatment with adalimumab should be combined with methotrexate in patients who tolerate methotrexate to avoid potential ADAb formation and related treatment failure in JIA-uveitis (II). If treatment failure occurs, ADAb and serum trough levels should be measured (II).[69,107,109,117] I have not been able to determine a therapeutic trough level for adalimumab nor do I know which individual variables besides ADAbs impact the treatment response in JIA-uveitis (II). Therefore, clinical response should be the primary guiding factor, instead of adalimumab trough level or anti-adalimumab antibody titer, when modifying adalimumab treatment.

7.3. FAI IMPLANTATION

If biologic treatment, short-term systemic glucocorticoid treatment, and short-acting intravitreal glucocorticoids fail to control macular oedema in JIA-uveitis, a longer-lasting sustained-release glucocorticoid implant can be considered as a rescue therapy (III). The potential benefits of sustained-release glucocorticoid implants should be weighed against the high complication rates associated with them (III).[187–189]

The 0.59 mg FAI that I studied is not commercially available any longer (III). Lower-dose 0.18 mg FAIs seem to have some impact on macular thickness in adults but have not been studied in children.[190] Sustained-

release dexamethasone implants seem rather short-acting for the treatment of JIA-uveitis-related macular oedema.[76,77,187] Fortunately, studies have shown that biologic treatment can be effective for patients with JIA-uveitis and related chronic macular oedema.[56,138] Furthermore, antirheumatic treatment is as effective as a 0.59 mg FAI in treating uveitis-related macular oedema in adults according to the The Multicenter Uveitis Steroid Treatment Trial.[182] A high-dose biologic treatment should be considered if a standard dose does not control JIA-uveitis or macular oedema related to it.[18]

Based on the current research,[18,56,138,180,182] resistant macular oedema related to JIA-uveitis should be treated with biologic treatment. If biologic treatment fails to control the macular oedema, sustained-release glucocorticoid implants can be considered (III).[25,77,182]

7.4. CATARACT SURGERY

Cataract extraction with primary IOL implantation should not be performed in eyes with active JIA-uveitis. The uveitis should be well-controlled 3 to 12 months prior the surgery (IV). Antirheumatic medication should be considered for better control of uveitis to improve the visual prognosis of JIA-uveitis in general and also when related to cataract surgery.[31,32]

Primary IOL implantation at cataract surgery produces good visual acuity results in eyes with good control of uveitis. Posterior capsulotomy and anterior vitrectomy may be reserved for patients younger than 4 years of age and for eyes with vitreous pathology. Intravitreal triamcinolone is not required to control the postoperative inflammatory reaction in well-controlled uveitis. Ocular complications are common after JIA-uveitis-related cataract surgery. Frequent follow-up visits should be scheduled after surgery to detect uveitis relapses, IOP problems, and macular oedema (IV). OCT imaging should be used routinely to detect and record macular oedema.[144]

Focusing on antirheumatic treatment and avoiding glucocorticoids should result in less demand for cataract surgery at a young age in JIA-uveitis.[79,140]

8. CONCLUSIONS AND FUTURE PROSPECTS

Treatment of JIA-related uveitis is a multifaceted challenge.

The first step in improving the treatment results and visual prognosis of JIA-uveitis is early diagnosis, which is why all patients with JIA must be screened regularly for uveitis.[4,8]

Long-term strict control of inflammation is the second step in improving the prognosis.[9,16] For now it is known that methotrexate and biologic treatment in combination with methotrexate can provide good control of inflammation in JIA-uveitis with less complications than treatment with glucocorticoids.[67,68,83] Combining biologic adalimumab treatment with methotrexate is more beneficial than monotherapy with either one of them according to a previous study[67] and my study (II). However, studies comparing different approaches to the systemic antirheumatic and topical glucocorticoid treatment are needed.

Thirdly, reducing the risk of ocular complications is important because ocular complications are associated with reduced vision and blindness in JIA-uveitis.[8,9,13,19,82] Glucocorticoid-sparing antirheumatic treatment is beneficial in reducing the complication rate and in improving the visual prognosis of JIA-uveitis.[9,16,82]

The final step in the care of patients with JIA-uveitis is to treat complications with the best available treatment approach. My study shows that JIA-uveitis-related complications such as cataract, glaucoma, and macular oedema can be treated with favourable outcomes in most eyes with JIA-uveitis (I,III,IV).

Despite recent advances in the treatment of JIA-uveitis, visual prognosis is still guarded or poor in eyes with uveitis-related complications and high-grade inflammation (I,III,IV).[2,47,132] Clinical practice with treatment focus in antirheumatics gives hope that better control of uveitis and simultaneous reduction in glucocorticoid treatment can improve the visual prognosis in JIA-uveitis in the future.

9. REFERENCES

1. Foster CS, Kothari S, Anesi SD, Vitale AT, Chu D, Metzinger JL, Cerón O. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. *Surv Ophthalmol*. 2016;61(1):1-17. doi:10.1016/j.survophthal.2015.07.001
2. Tomkins-Netzer O, Talat L, Bar A, Lula A, Taylor SRJ, Joshi L, Lightman S. Long-term clinical outcome and causes of vision loss in patients with uveitis. *Ophthalmology*. Published online 2014. doi:10.1016/j.ophtha.2014.07.007
3. Vitale AT, Graham E, de Boer JH. Juvenile idiopathic arthritis-associated uveitis: Clinical features and complications, risk factors for severe course, and visual outcome. *Ocul Immunol Inflamm*. 2013;21(6):478-485. doi:10.3109/09273948.2013.815785
4. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology*. 2007;46(6):1015-1019. doi:10.1093/rheumatology/kem053
5. Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: A prospective study. *Ophthalmology*. Published online 2001. doi:10.1016/S0161-6420(01)00773-4
6. Nordal E, Christoffersen T, Aalto K, Berntson L, Fasth A, Herlin T, Nielsen S, Peltoniemi S, Straume B, Zak M, Rygg M. Incidence and predictors of uveitis in juvenile idiopathic arthritis in a Nordic long-term cohort study. *Pediatr Rheumatol*. 2017;15(1). doi:10.1186/s12969-017-0195-8
7. Kotaniemi K, Savolainen A, Karma A, Aho K. Recent advances in uveitis of juvenile idiopathic arthritis. *Surv Ophthalmol*. 2003;48(5):489-502. doi:10.1016/S0039-6257(03)00084-5
8. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol*. 2002;86(1):51-56. doi:10.1136/bjo.86.1.51
9. Gregory AC, Kempen JH, Daniel E, Kaçmaz RO, Foster CS, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: The SITE Study. *Ophthalmology*. 2013;120(1):186-192. doi:10.1016/j.ophtha.2012.07.052
10. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. *Br J Ophthalmol*. 1996;80(4):332-336. doi:10.1136/bjo.80.4.332
11. De Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. *Br J Ophthalmol*. 2003;87(7):879-884. doi:10.1136/bjo.87.7.879
12. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis- associated uveitis. *Ophthalmology*. 1997;104(2):236-244. doi:10.1016/S0161-6420(97)30329-7
13. Angeles-Han ST, McCracken C, Yeh S, Jenkins K, Stryker D, Rouster-Stevens K, Vogler LB, Lambert SR, Drews-Botsch C, Prahalad S. Characteristics of a cohort of children with juvenile idiopathic arthritis and JIA-associated uveitis. *Pediatr Rheumatol*. 2015;13(1). doi:10.1186/s12969-015-0018-8
14. Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, Gepstein R, Heiligenhaus A, Pilkington CA, Simonini G, Uziel Y, Vastert SJ, Wulffraat NM, Haasnoot A-M, Walscheid K, Pálinkás A, Pattani R, Györgyi Z, Kozma R, Boom V, Ponyi A, Ravelli A, Ramanan AV. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Ann Rheum Dis*. 2018;77(8):1107-1117. doi:10.1136/annrheumdis-2018-213131
15. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, Baus H, Becker M, Bertram B, Dannecker G, Deuter C, Foeldvari I, Frosch M, Ganser G,

Gaubitz M, Gerdes G, Horneff G, Illhardt A, Mackensen F, Minden K, Pleyer U, Schneider M, Wagner N, Zierhut M, German Ophthalmological Society, Society for Childhood and Adolescent Rheumatology, German Society for Rheumatology. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int*. 2012;32(5):1121-1133. doi:10.1007/s00296-011-2126-1

16. Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: Incidence of ocular complications and visual acuity loss. *Am J Ophthalmol*. 2007;143(5):840-846.e2. doi:10.1016/j.ajo.2007.01.033
17. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509-516. doi:10.1016/j.ajo.2005.03.057
18. Angeles-Han ST, Ringold S, Beukelman T, Lovell D, Cuello CA, Becker ML, Colbert RA, Feldman BM, Holland GN, Ferguson PJ, Gewanter H, Guzman J, Horonjeff J, Nigrovic PA, Ombrello MJ, Passo MH, Stoll ML, Rabinovich CE, Sen HN, Schneider R, Halyabar O, Hays K, Shah AA, Sullivan N, Szymanski AM, Turgunbaev M, Turner A, Reston J. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis–associated uveitis. *Arthritis Care Res*. 2019;71(6):703-716. doi:10.1002/acr.23871
19. Woreta F, Thorne JE, Jabs DA, Kedhar SR, Dunn JP. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol*. 2007;143(4):647-655.e1. doi:10.1016/j.ajo.2006.11.025
20. Foster CS, Havrlikova K, Baltatzis S, Christen WG, Merayo-Lloves J. Secondary glaucoma in patients with juvenile rheumatoid arthritis-associated iridocyclitis. *Acta Ophthalmol Scand*. 2000;78(5):576-579. doi:10.1034/j.1600-0420.2000.078005576.x
21. Heinz C, Koch JM, Heiligenhaus A. Trabeculectomy or modified deep sclerectomy in juvenile uveitic glaucoma. *J Ophthalmic Inflamm Infect*. 2011;1(4):165-170. doi:10.1007/s12348-011-0039-5
22. Ho CL, Wong EYM, Walton DS. Goniosurgery for glaucoma complicating chronic childhood uveitis. *Arch Ophthalmol*. 2004;122(6):838. doi:10.1001/archopht.122.6.838
23. Välimäki J. Molteno implantation for secondary glaucoma in juvenile rheumatoid arthritis. *Arch Ophthalmol*. 1997;115(10):1253. doi:10.1001/archopht.1997.01100160423005
24. Goldhardt R, Rosen BS. Uveitic macular edema: treatment update. *Curr Ophthalmol Rep*. 2016;4(1):30-37. doi:10.1007/s40135-016-0090-3
25. Sallam A, Comer RM, Chang JH, Grigg JR, Andrews R, McCluskey PJ, Lightman S. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. *Arch Ophthalmol*. 2008;126(2):200. doi:10.1001/archophthalmol.2007.59
26. de Boer J, Steijaert A, van den Bor R, Stellato R, Ossewaarde-van Norel J. Development of macular edema and impact on visual acuity in uveitis associated with juvenile idiopathic arthritis. *Ocul Immunol Inflamm*. 2015;23(1):67-73. doi:10.3109/09273948.2013.871566
27. Paroli MP, Fabiani C, Spinucci G, Abicca I, Sapia A, Spadea L. Severe macular edema in patients with juvenile idiopathic arthritis-related uveitis. *Case Rep Ophthalmol Med*. 2013;2013:1-5. doi:10.1155/2013/803989
28. Angeles-Han S, Yeh S. Prevention and management of cataracts in children with juvenile idiopathic arthritis-associated uveitis. *Curr Rheumatol Rep*. 2012;14(2):142-149. doi:10.1007/s11926-011-0229-z
29. Kotaniemi K, Penttilä H. Intraocular lens implantation in patients with juvenile idiopathic arthritis-associated uveitis. *Ophthalmic Res*. 2006;38(6):318-323. doi:10.1159/000096225
30. Grajewski RS, Zurek-Imhoff B, Roesel M, Heinz C, Heiligenhaus A. Favourable outcome after cataract surgery with IOL implantation in uveitis associated with juvenile idiopathic arthritis. *Acta Ophthalmol (Copenh)*. 2012;90(7):657-662. doi:10.1111/j.1755-3768.2011.02110.x

31. Magli A, Forte R, Rombetto L, Alessio M. Cataract management in juvenile idiopathic arthritis: simultaneous versus secondary intraocular lens implantation. *Ocul Immunol Inflamm*. 2014;22(2):133-137. doi:10.3109/09273948.2013.834062
32. Quiñones K, Cervantes-Castañeda RA, Hynes AY, Daoud YJ, Foster CS. Outcomes of cataract surgery in children with chronic uveitis. *J Cataract Refract Surg*. 2009;35(4):725-731. doi:10.1016/j.jcrs.2008.12.014
33. Nussenblatt RB. The natural history of uveitis. *Int Ophthalmol*. 1990;14(5-6):303-308. doi:10.1007/BF00163549
34. Jabs DA, Busingye J. Approach to the diagnosis of the uveitides. *Am J Ophthalmol*. 2013;156(2):228-236. doi:10.1016/j.ajo.2013.03.027
35. Bro T, Tallstedt L. Epidemiology of uveitis in a region of southern Sweden. *Acta Ophthalmol (Copenh)*. 2020;98(1):32-35. doi:10.1111/aos.14130
36. Forrester JV, Klaska IP, Yu T, Kuffova L. Uveitis in mouse and man. *Int Rev Immunol*. 2013;32(1):76-96. doi:10.3109/08830185.2012.747524
37. Siiskonen M, Hirn I, Pesälä R, Hautala T, Ohtonen P, Hautala N. Prevalence, incidence and epidemiology of childhood uveitis. *Acta Ophthalmol (Copenh)*. Published online June 26, 2020. doi:10.1111/aos.14535
38. Paivonsalo-Hietanen T, Tuominen J, Matti Saari K. Uveitis in children: population-based study in Finland. *Acta Ophthalmol Scand*. 2000;78(1):84-88. doi:10.1034/j.1600-0420.2000.078001084.x
39. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur A-M, Suarez-Almazor ME, Woo P, International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.
40. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine*. 2014;81(2):112-117. doi:10.1016/j.jbspin.2013.09.003
41. Rypdal V, Glerup M, Songstad NT, Bertelsen G, Christoffersen T, Arnstad ED, Aalto K, Berntson L, Fasth A, Herlin T, Ekelund M, Peltoniemi S, Toftedal P, Nielsen S, Leinonen S, Bangsgaard R, Nielsen R, Rygg M, Nordal E. Uveitis in juvenile idiopathic arthritis: 18-year outcome in the population-based Nordic cohort study. *Ophthalmology*. Published online August 2020. doi:10.1016/j.ophtha.2020.08.024
42. Tugal-Tutkun I. Pediatric uveitis. *J Ophthalmic Vis Res*. 2011;6(4):259-269.
43. Quartier P, Baptiste A, Despert V, Allain-Launay E, Koné-Paut I, Belot A, Kodjikian L, Monnet D, Weber M, Elie C, Bodaghi B. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis*. 2018;77(7):1003-1011. doi:10.1136/annrheumdis-2017-212089
44. Papadopoulou C, Kostik M, Böhm M, Nieto-Gonzalez JC, Gonzalez-Fernandez MI, Pistorio A, Martini A, Ravelli A. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. *J Pediatr*. Published online 2013. doi:10.1016/j.jpeds.2013.03.047
45. Tappeiner C, Schenck S, Niewerth M, Heiligenhaus A, Minden K, Klotsche J. Impact of anti-inflammatory treatment on the onset of uveitis in juvenile idiopathic arthritis: longitudinal analysis from a nationwide pediatric rheumatology database. *Arthritis Care Res*. 2016;68(1):46-54. doi:10.1002/acr.22649
46. Kotaniemi K, Aho K, Kotaniemi A. Uveitis as a cause of visual loss in arthritides and comparable conditions. *J Rheumatol*. Published online 2001.
47. Kalinina Ayuso V, Ten Cate H, van der Does P, Rothova A, de Boer J. Male gender as a risk factor for complications in uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol*. 2010;149(6):994-999.e5. doi:10.1016/j.ajo.2010.01.016
48. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol*. 2011;151(2):217-222. doi:10.1016/j.ajo.2010.08.021
49. Forrester JV, Kuffova L, Dick AD. Autoimmunity, autoinflammation, and infection in uveitis. *Am J Ophthalmol*. 2018;189:77-85. doi:10.1016/j.ajo.2018.02.019
50. Caspi RR. A look at autoimmunity and inflammation in the eye. *J Clin Invest*. 2010;120(9):3073-3083. doi:10.1172/JCI42440

51. Horai R, Caspi RR. Cytokines in autoimmune uveitis. *J Interferon Cytokine Res*. 2011;31(10):733-744. doi:10.1089/jir.2011.0042
52. Chang PY, Giuliari GP, Shaikh M, Thakuria P, Makhoul D, Foster CS. Mycophenolate mofetil monotherapy in the management of paediatric uveitis. *Eye*. 2011;25(4):427-435. doi:10.1038/eye.2011.23
53. Tappeiner C, Heinz C, Ganser G, Heiligenhaus A. Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? *J Rheumatol*. 2012;39(6):1294.2-1295. doi:10.3899/jrheum.120010
54. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. *Eye*. 2009;23(5):1192-1198. doi:10.1038/eye.2008.174
55. Tappeiner C, Miserocchi E, Bodaghi B, Kotaniemi K, Mackensen F, Gerloni V, Quartier P, Lutz T, Heiligenhaus A. Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2015;42(4):706-711. doi:10.3899/jrheum.140410
56. Calvo-Río V, Santos-Gómez M, Calvo I, González-Fernández MI, López-Montesinos B, Mesquida M, Adán A, Hernández MV, Maíz O, Atanes A, Bravo B, Modesto C, Díaz-Cordovés G, Palmou-Fontana N, Loricera J, González-Vela MC, Demetrio-Pablo R, Hernández JL, González-Gay MA, Blanco R. Anti–interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis–associated uveitis refractory to anti–tumor necrosis factor therapy: a multicenter study of twenty-five patients. *Arthritis Rheumatol Hoboken NJ*. 2017;69(3):668-675. doi:10.1002/art.39940
57. Birolo C, Zannin ME, Arsenyeva S, Cimaz R, Miserocchi E, Dubko M, Deslandre CJ, Falcini F, Alessio M, La Torre F, Denisova E, Martini G, Nikishina I, Zulian F. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. *J Rheumatol*. 2016;43(11):2068-2073. doi:10.3899/jrheum.151389
58. Tappeiner C, Mesquida M, Adán A, Anton J, Ramanan AV, Carreno E, Mackensen F, Kotaniemi K, de Boer JH, Bou R, de Vicuña CG, Heiligenhaus A. Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2016;43(12):2183-2188. doi:10.3899/jrheum.160231
59. Walscheid K, Neekamp L, Heiligenhaus A, Weinhage T, Heinz C, Foell D. Increased circulating proinflammatory T lymphocytes in children with different forms of anterior uveitis: results from a pilot study. *Ocul Immunol Inflamm*. 2019;27(5):788-797. doi:10.1080/09273948.2018.1467464
60. Mehta AK, Gracias DT, Croft M. TNF activity and T cells. *Cytokine*. Published online 2018. doi:10.1016/j.cyto.2016.08.003
61. Walters HM, Pan N, Lehman TJA, Adams A, Kalliolias GD, Zhu YS, Santiago F, Nguyen J, Sitaras L, Cunningham-Rundles S, Walsh TJ, Toussi SS. The impact of disease activity and tumour necrosis factor-α inhibitor therapy on cytokine levels in juvenile idiopathic arthritis. *Clin Exp Immunol*. 2016;184(3):308-317. doi:10.1111/cei.12782
62. Ooi KG-J, Galatowicz G, Calder VL, Lightman SL. Cytokines and chemokines in uveitis: is there a correlation with clinical phenotype? *Clin Med Res*. 2006;4(4):294-309. doi:10.3121/cmr.4.4.294
63. Santos Lacomba M, Marcos Martín C, Gallardo Galera JM, Gómez Vidal MA, Collantes Estévez E, Ramírez Chamond R, Omar MM. Aqueous humor and serum tumor necrosis factor-α in clinical uveitis. *Ophthalmic Res*. Published online 2001. doi:10.1159/000055677
64. Wakefield D, Lloyd A. The role of cytokines in the pathogenesis of inflammatory eye disease. *Cytokine*. 1992;4(1):1-5. doi:10.1016/1043-4666(92)90028-p
65. Dick AD, Duncan L, Hale G, Waldmann H, Isaacs J. Neutralizing TNF-alpha activity modulates T-cell phenotype and function in experimental autoimmune uveoretinitis. *J Autoimmun*. 1998;11(3):255-264. doi:10.1006/jaut.1998.0197
66. Sartani G, Silver PB, Rizzo LV, Chan CC, Wiggert B, Mastorakos G, Caspi RR. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. *Invest Ophthalmol Vis Sci*. 1996;37(11):2211-2218.
67. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, Hardwick B, Hickey H, Hughes D, Woo P, Benton D, Edelsten C, Beresford MW.

Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med*. 2017;376(17):1637-1646. doi:10.1056/NEJMoa1614160
68. Cecchin V, Zannin ME, Ferrari D, Pontikaki I, Miserocchi E, Paroli MP, Bracaglia C, Marafon DP, Pastore S, Parentin F, Simonini G, De Libero C, Falcini F, Petaccia A, Filocamo G, De Marco R, La Torre F, Guerriero S, Martino S, Comacchio F, Muratore V, Martini G, Vittadello F, Zulian F. Longterm safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2018;45(8):1167-1172. doi:10.3899/jrheum.171006
69. Imagawa T, Takei S, Umebayashi H, Yamaguchi K, Itoh Y, Kawai T, Iwata N, Murata T, Okafuji I, Miyoshi M, Onoe Y, Kawano Y, Kinjo N, Mori M, Mozaffarian N, Kupper H, Santra S, Patel G, Kawai S, Yokota S. Efficacy, pharmacokinetics, and safety of adalimumab in pediatric patients with juvenile idiopathic arthritis in Japan. *Clin Rheumatol*. Published online 2012. doi:10.1007/s10067-012-2082-5
70. Klotsche J, Niewerth M, Haas J-P, Huppertz H-I, Zink A, Horneff G, Minden K. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). *Ann Rheum Dis*. 2016;75(5):855-861. doi:10.1136/annrheumdis-annrheumdis-2014-206747
71. Madson KL, Moore TL, Lawrence JM, Osborn TG. Cytokine levels in serum and synovial fluid of patients with juvenile rheumatoid arthritis. *J Rheumatol*. 1994;21(12):2359-2363.
72. Mangge H, Kenzian H, Gallistl S, Neuwirth G, Liebmann P, Kaulfersch W, Beaufort F, Muntean W, Schauenstein K. Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. *Arthritis Rheum*. 1995;38(2):211-220. doi:10.1002/art.1780380209
73. Yilmaz M, Kendirli SG, Altintas D, Bingöl G, Antmen B. Cytokine levels in serum of patients with juvenile rheumatoid arthritis. *Clin Rheumatol*. 2001;20(1):30-35. doi:10.1007/s100670170100
74. Tappeiner C, Heinz C, Roesel M, Heiligenhaus A. Elevated laser flare values correlate with complicated course of anterior uveitis in patients with juvenile idiopathic arthritis. *Acta Ophthalmol (Copenh)*. 2011;89(6):e521-e527. doi:10.1111/j.1755-3768.2011.02162.x
75. Oray M, Tuğal-Tutkun İ. Treatment of juvenile idiopathic arthritis-associated uveitis. *Türk Oftalmol Derg*. 2016;46(2):77-82. doi:10.4274/tjo.09581
76. Sella R, Oray M, Friling R, Umar L, Tugal-Tutkun I, Kramer M. Dexamethasone intravitreal implant (Ozurdex®) for pediatric uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(10):1777-1782. doi:10.1007/s00417-015-3124-x
77. Pichi F, Nucci P, Baynes K, Lowder CY, Srivastava SK. Sustained-release dexamethasone intravitreal implant in juvenile idiopathic arthritis-related uveitis. *Int Ophthalmol*. 2017;37(1):221-228. doi:10.1007/s10792-016-0265-9
78. Kothari S, Foster CS, Pistilli M, Liesegang TL, Daniel E, Sen HN, Suhler EB, Thorne JE, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Lawrence SD, Kempen JH, Systemic Immunosuppressive Therapy for Eye Diseases Research Group. The risk of intraocular pressure elevation in pediatric noninfectious uveitis. *Ophthalmology*. 2015;122(10):1987-2001. doi:10.1016/j.ophtha.2015.06.041
79. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. *Ophthalmology*. 2010;117(7):1436-1441. doi:10.1016/j.ophtha.2009.12.003
80. Buchman AL. Side effects of corticosteroid therapy. *J Clin Gastroenterol*. 2001;33(4):289-294. doi:10.1097/00004836-200110000-00006
81. Waljee AK, Wiitala WL, Govani S, Stidham R, Saini S, Hou J, Feagins LA, Khan N, Good CB, Vijan S, Higgins PDR. Corticosteroid use and complications in a US inflammatory bowel disease cohort. *PloS One*. 2016;11(6):e0158017. doi:10.1371/journal.pone.0158017
82. Stroh IG, Moradi A, Burkholder BM, Hornbeak DM, Leung TG, Thorne JE. Occurrence of and risk factors for ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm*. 2017;25(4):503-512. doi:10.3109/09273948.2016.1142573
83. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: A systematic review and meta-

analysis approach. *Rheumatol U K*. Published online 2013. doi:10.1093/rheumatology/kes186
84. Goebel JC, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. *Br J Ophthalmol*. Published online 2011. doi:10.1136/bjo.2009.173542
85. Bichler J, Benseler SM, Krumrey-Langkammerer M, Haas J-P, Hügle B. Leflunomide is associated with a higher flare rate compared to methotrexate in the treatment of chronic uveitis in juvenile idiopathic arthritis. *Scand J Rheumatol*. 2015;44(4):280-283. doi:10.3109/03009742.2015.1013983
86. Kempen JH, Daniel E, Dunn JP, Foster CS, Gangaputra S, Hanish A, Helzlsouer KJ, Jabs DA, Kaçmaz RO, Levy-Clarke GA, Liesegang TL, Newcomb CW, Nussenblatt RB, Pujari SS, Rosenbaum JT, Suhler EB, Thorne JE. Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. *BMJ*. 2009;339:b2480. doi:10.1136/bmj.b2480
87. Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M, Scallon B, Moore MA, Vilcek J, Daddona P, Ghrayeb J. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Mol Immunol*. Published online 1993. doi:10.1016/0161-5890(93)90106-L
88. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: Lessons learned, unresolved issues and future directions. In: *TNF Pathophysiology: Molecular and Cellular Mechanisms*. ; 2010. doi:10.1159/000289205
89. Cunha-Vaz JG. The blood-ocular barriers: Past, present, and future. *Doc Ophthalmol*. Published online 1997. doi:10.1007/BF02569055
90. Luna JD, Chan CC, Derevjanik NL, Mahlow J, Chiu C, Peng B, Tobe T, Campochiaro PA, Vinores SA. Blood-retinal barrier (BRB) breakdown in experimental autoimmune uveoretinitis: comparison with vascular endothelial growth factor, tumor necrosis factor alpha, and interleukin-1beta-mediated breakdown. *J Neurosci Res*. 1997;49(3):268-280. doi:10.1002/(sici)1097-4547(19970801)49:3<268::aid-jnr2>3.0.co;2-a
91. Kotaniemi K, Säilä H, Kautiainen H. Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. *Clin Ophthalmol*. Published online 2011.
92. Llorenç V, Mesquida M, Sainz de la Maza M, Blanco R, Calvo V, Maíz O, Blanco A, de Dios-Jiménez de Aberásturi JR, Adán A. Certolizumab pegol, a new anti-TNF-α in the armamentarium against ocular inflammation. *Ocul Immunol Inflamm*. 2016;24(2):167-172. doi:10.3109/09273948.2014.967779
93. Reiff A, Takei S, Sadeghi S, Stout A, Shaham B, Bernstein B, Gallagher K, Stout T. Etanercept therapy in children with treatment-resistant uveitis. *Arthritis Rheum*. Published online 2001. doi:10.1002/1529-0131(200106)44:6<1411::AID-ART235>3.0.CO;2-O
94. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology*. 2005;44(8):1008-1011. doi:10.1093/rheumatology/keh658
95. Smith JA, Thompson DJS, Whitcup SM, Suhler E, Clarke G, Smith S, Robinson M, Kim J, Barron KS. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum*. 2005;53(1):18-23. doi:10.1002/art.20904
96. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis*. 2006;66(4):548-550. doi:10.1136/ard.2006.058248
97. Ardoin SP, Kredich D, Rabinovich E, Schanberg LE, Jaffe GJ. Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol*. 2007;144(6):844-849.e1. doi:10.1016/j.ajo.2007.08.018
98. William M, Faez S, Papaliodis GN, Lobo A-M. Golimumab for the treatment of refractory juvenile idiopathic arthritis-associated uveitis. *J Ophthalmic Inflamm Infect*. Published online 2012. doi:10.1007/s12348-012-0081-y
99. Palmou-Fontana N, Calvo-Río V, Martín-Varillas JL, Fernández-Díaz C, Mesquida M, Adán A, Hernández MV, Cordero-Coma M, Maiz Alonso O, Díaz-Valle D, Fernández-Cid C, Ruiz-Moreno O, Hernández JL, González-Gay MA, Blanco R. Golimumab in

refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review. *Clin Exp Rheumatol*. Published online 2018.
100. Nagy A, Mátrai P, Hegyi P, Alizadeh H, Bajor J, Czopf L, Gyöngyi Z, Kiss Z, Márta K, Simon M, Szilágyi ÁL, Veres G, Mosdósi B. The effects of TNF-alpha inhibitor therapy on the incidence of infection in JIA children: a meta-analysis. *Pediatr Rheumatol Online J*. 2019;17(1):4. doi:10.1186/s12969-019-0305-x
101. Toussi SS, Pan N, Walters HM, Walsh TJ. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-α inhibitors: systematic review of the literature. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2013;57(9):1318-1330. doi:10.1093/cid/cit489
102. Calzada-Hernández J, Anton-López J, Bou-Torrent R, Iglesias-Jiménez E, Ricart-Campos S, Martín de Carpi J, Carmen García de Vicuña Muñoz de la Nava, Torrente-Segarra V, Sánchez-Manubens J, Giménez-Roca C, Rozas-Quesada L, Juncosa-Morros MT, Fortuny C, Noguera-Julian A. Tuberculosis in pediatric patients treated with anti-TNFα drugs: a cohort study. *Pediatr Rheumatol Online J*. 2015;13:54. doi:10.1186/s12969-015-0054-4
103. Kumar N, Abboud H. Iatrogenic CNS demyelination in the era of modern biologics. *Mult Scler*. 2019;15(Feb).
104. Alexandre B, Vandermeeren Y, Dewit O, Moreels T, de Boer N, Dhar A, Ziady C, Shitrit ABG, Steinwurz F, Jojic N, Costantino G, Bihin B, Rahier JF, Katsanos KH. Optic neuritis associated or not with TNF antagonists in patients with inflammatory bowel disease. *J Crohns Colitis*. Published online 2016. doi:10.1093/ecco-jcc/jjw003
105. Bernatsky S, Rosenberg AM, Oen KG, Duffy CM, Ramsey-Goldman R, Labrecque J, St. Pierre Y, Clarke AE. Malignancies in juvenile idiopathic arthritis: A preliminary report. *J Rheumatol*. Published online 2011. doi:10.3899/jrheum.100711
106. Beukelman T, Xie F, Chen L, Horton DB, Lewis JD, Mamtani R, Mannion MM, Saag KG, Curtis JR. Risk of malignancy associated with paediatric use of tumour necrosis factor inhibitors. *Ann Rheum Dis*. Published online 2018. doi:10.1136/annrheumdis-2017-212613
107. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: A systematic review of the literature with a meta-analysis. *Ann Rheum Dis*. Published online 2013. doi:10.1136/annrheumdis-2012-202220
108. Laine J, Sakari Jokiranta T, Eklund KK, Väkeväinen M, Puolakka K. Cost-effectiveness of routine measuring of serum drug concentrations and anti-drug antibodies in treatment of rheumatoid arthritis patients with TNF-α blockers. *Biol Targets Ther*. Published online 2016. doi:10.2147/BTT.S96982
109. Wang S-L, Hauenstein S, Ohrmund L, Shringarpure R, Salbato J, Reddy R, McCowen K, Shah S, Lockton S, Chuang E, Singh S. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal*. 2013;78-79:39-44. doi:10.1016/j.jpba.2013.01.031
110. Krishna M, Nadler SG. Immunogenicity to biotherapeutics - the role of anti-drug immune complexes. *Front Immunol*. 2016;7:21. doi:10.3389/fimmu.2016.00021
111. Pratt K. Anti-drug antibodies: Emerging approaches to predict, reduce or reverse biotherapeutic immunogenicity. *Antibodies*. 2018;7(2):19. doi:10.3390/antib7020019
112. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz M-T, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur A-M, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, Giannini EH, Paediatric Rheumatology International Trials Organisation. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2007;56(9):3096-3106. doi:10.1002/art.22838
113. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz H-I, Olson NY, Medich JR, Carcereri-De-Prati R, McIlraith MJ, Giannini EH, Martini A, Pediatric Rheumatology Collaborative Study Group, Pediatric Rheumatology International Trials Organisation. Adalimumab

with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med*. 2008;359(8):810-820. doi:10.1056/NEJMoa0706290
114. Cordero-Coma M, Calleja-Antolín S, Garzo-García I, Nuñez-Garnés AM, Álvarez-Castro C, Franco-Benito M, Ruiz de Morales JG. Adalimumab for treatment of noninfectious uveitis: immunogenicity and clinical relevance of measuring serum drug levels and antidrug antibodies. *Ophthalmology*. 2016;123(12):2618-2625. doi:10.1016/j.ophtha.2016.08.025
115. Murias S, Alcobendas R, Pascual-Salcedo D, Remesal A, Peralta J, Merino R. Anti-adalimumab antibodies in paediatric rheumatology patients: a pilot experience. *Rheumatology*. 2014;53(11):2124-2126. doi:10.1093/rheumatology/keu305
116. Skrabl-Baumgartner A, Seidel G, Langner-Wegscheider B, Schlagenhauf A, Jahnel J. Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis-associated uveitis. *Arch Dis Child*. 2019;104(3):246-250. doi:10.1136/archdischild-2018-315060
117. Skrabl-Baumgartner A, Erwa W, Muntean W, Jahnel J. Anti-adalimumab antibodies in juvenile idiopathic arthritis: frequent association with loss of response. *Scand J Rheumatol*. 2015;44(5):359-362. doi:10.3109/03009742.2015.1022213
118. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Wolbink GJ, de Vries N, Tak PP, Dijkmans B a. C, Crusius JBA, van der Horst-Bruinsma IE. Anti-adalimumab antibodies in rheumatoid arthritis patients are associated with interleukin-10 gene polymorphisms. *Arthritis Rheum*. 2009;60(8):2541-2542. doi:10.1002/art.24709
119. Jani M, Barton A, Warren RB, Griffiths CEM, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatol Oxf Engl*. 2014;53(2):213-222. doi:10.1093/rheumatology/ket260
120. Eklund K, Havana M, Kröger L, Jokiranta TS, Valtanen S, Ho D. FRI0111 Analysis of real-life infliximab and adalimumab data: drug switching and fate of antidrug antibodies and trough levels over time. EULAR 2018. doi:10.1136/annrheumdis-2018-eular.3052
121. Eklund K, Valtanen S, Havana M, Kröger L, Ho D, Jokiranta S. SAT0152 Real-life infliximab and adalimumab trough level and anti-drug antibody measurements in rheumatology: the finnish experience. EULAR 2017. doi:10.1136/annrheumdis-2017-eular.5943
122. Kosmač M, Avčin T, Toplak N, Simonini G, Cimaz R, Šerbec VČ. Exploring the binding sites of anti-infliximab antibodies in pediatric patients with rheumatic diseases treated with infliximab. *Pediatr Res*. Published online 2011. doi:10.1203/PDR.0b013e318208451d
123. Aeschlimann FA, Angst F, Hofer KD, Cannizzaro Schneider E, Schroeder-Kohler S, Lauener R, van der Kleij D, Rispens T, Saurenmann RK. Prevalence of anti-infliximab antibodies and their associated co-factors in children with refractory arthritis and/or uveitis: A retrospective longitudinal cohort study. *J Rheumatol*. 2017;44(3):334-341. doi:10.3899/jrheum.160072
124. Doeleman MJH, van Maarseveen EM, Swart JF. Immunogenicity of biologic agents in juvenile idiopathic arthritis: a systematic review and meta-analysis. *Rheumatology*. 2019;58(10):1839-1849. doi:10.1093/rheumatology/kez030
125. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann Rheum Dis*. 2012;71(11):1914-1915. doi:10.1136/annrheumdis-2012-201544
126. Bitoun S, Nocturne G, Ly B, Krzysiek R, Roques P, Pruvost A, Paoletti A, Pascaud J, Dönnes P, Florence K, Gleizes A, Hincelin-Mery A, Allez M, Hacein-Bey-Abina S, Mackay F, Pallardy M, Le Grand R, Mariette X. Methotrexate and BAFF interaction prevents immunization against TNF inhibitors. *Ann Rheum Dis*. Published online June 23, 2018:annrheumdis-2018-213403. doi:10.1136/annrheumdis-2018-213403
127. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). *Rheumatol Oxf Engl*. Published online 2011. doi:10.1093/rheumatology/ker107
128. Santos Gómez M, Calvo-Río V, Blanco R, Calvo I, Maíz O, Atanes A, Bravo B, Modesto C, Díaz Soriano G, Riancho-Zarrabeitia L, Palmaou-Fontana N, González-Gay MA. THU0523 Tocilizumab in refractory uveitis associated to juvenile idiopathic arthritis.

multicenter study of 13 cases. *Ann Rheum Dis*. 2015;74(Suppl 2):389.3-390. doi:10.1136/annrheumdis-2015-eular.5617
129. Tanaka T, Narazaki M, Kishimoto T. Anti-interleukin-6 receptor antibody, tocilizumab, for the treatment of autoimmune diseases. *FEBS Lett*. 2011;585(23):3699-3709. doi:10.1016/j.febslet.2011.03.023
130. Kanski JJ, Shun-Shin GA. Systemic uveitis syndromes in childhood: an analysis of 340 cases. *Ophthalmology*. 1984;91(10):1247-1252. doi:10.1016/S0161-6420(84)34177-X
131. Kotaniemi K, Sihto-Kauppi K. Occurrence and management of ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis: An observational series of 104 patients. *Clin Ophthalmol Auckl NZ*. Published online 2007.
132. Kotaniemi K, Sihto-Kauppi K, Salomaa P, Säilä H, Ristolainen L, Kauppi M. The frequency and outcome of uveitis in patients with newly diagnosed juvenile idiopathic arthritis in two 4-year cohorts from 1990-1993 and 2000-2003. *Clin Exp Rheumatol*. 2014;32(1):143-147.
133. Kump LI, Castañeda RAC, Androudi SN, Reed GF, Foster CS. Visual outcomes in children with juvenile idiopathic arthritis–associated uveitis. *Ophthalmology*. 2006;113(10):1874-1877. doi:10.1016/j.ophtha.2006.05.016
134. Paroli MP, Spinucci G, Fabiani C, Pivetti-Pezzi P. Retinal complications of juvenile idiopathic arthritis-related uveitis: A microperimetry and optical coherence tomography study. *Ocul Immunol Inflamm*. Published online 2010. doi:10.3109/09273940903311999
135. Daniel E, Pistilli M, Pujari SS, Kaçmaz RO, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Jabs DA, Levy-Clarke GA, Kempen JH. Risk of hypotony in noninfectious uveitis. *Ophthalmology*. 2012;119(11):2377-2385. doi:10.1016/j.ophtha.2012.05.032
136. Orès R, Terrada C, Errera M-H, Thorne JE, Doukhan R, Cassoux N, Penaud B, LeHoang P, Quartier PM, Bodaghi B. Laser flare photometry: A useful tool for monitoring patients with juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm*. Published online August 24, 2020:1-11. doi:10.1080/09273948.2020.1792511
137. Herbert HM, Viswanathan A, Jackson H, Lightman SL. Risk factors for elevated intraocular pressure in uveitis. *J Glaucoma*. 2004;13(2):96-99. doi:10.1097/00061198-200404000-00003
138. Calvo-Rio V, Blanco R, Diaz-Llopis M, Salom D, Garcia-Vicuna C, Cordero-Coma M, Ortego N, Suarez-De- Figueroa M, Fernandez-Cid JC, Calduch AF, Garcia-Aparicio AM, Benitez-Del-Castillo JM, Olea JL, Loricera J, Gonzalez-Gay MA. Response to adalimumab in 40 patients with refractory juvenile idiopathic arthritis-associated uveitis. A multicenter study. *Arthritis Rheum*. Published online 2012.
139. Kulik U, Wiklund A, Kugelberg M, Lundvall A. Long-term results after primary intraocular lens implantation in children with juvenile idiopathic arthritis-associated uveitis. *Eur J Ophthalmol*. 2019;29(5):494-498. doi:10.1177/1120672118799623
140. Sijssens KM, Rothova A, Van De Vijver DAMC, Stilma JS, De Boer JH. Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol*. 2007;144(4):574-579.e1. doi:10.1016/j.ajo.2007.06.030
141. BenEzra D, Cohen E. Cataract surgery in children with chronic uveitis. *Ophthalmology*. 2000;107(7):1255–1260. doi:10.1016/S0161-6420(00)00160-3
142. Phatak S, Lowder C, Pavesio C. Controversies in intraocular lens implantation in pediatric uveitis. *J Ophthalmic Inflamm Infect*. 2016;6(1). doi:10.1186/s12348-016-0079-y
143. Heinz C, Koch JM, Zurek-Imhoff B, Heiligenhaus A. Prevalence of uveitic secondary glaucoma and success of nonsurgical treatment in adults and children in a tertiary referral center. *Ocul Immunol Inflamm*. Published online 2009. doi:10.1080/09273940902913035
144. Ducos de Lahitte G, Terrada C, Tran THC, Cassoux N, LeHoang P, Kodjikian L, Bodaghi B. Maculopathy in uveitis of juvenile idiopathic arthritis: an optical coherence tomography study. *Br J Ophthalmol*. 2008;92(1):64-69. doi:10.1136/bjo.2007.120675
145. Sijssens KM, Los LI, Rothova A, Schellekens PAWJF, van de Does P, Stilma JS, de Boer HJ. Long-term ocular complications in aphakic versus pseudophakic eyes of children with juvenile idiopathic arthritis-associated uveitis. *Br J Ophthalmol*. 2010;94(9):1145-1149. doi:10.1136/bjo.2009.167379

146. Mehta S, Linton MM, Kempen JH. Outcomes of cataract surgery in patients with uveitis: a systematic review and meta-analysis. *Am J Ophthalmol*. 2014;158(4):676-692.e7. doi:10.1016/j.ajo.2014.06.018
147. Abela-Formanek C, Amon M, Kahraman G, Schauersberger J, Dunavoelgyi R. Biocompatibility of hydrophilic acrylic, hydrophobic acrylic, and silicone intraocular lenses in eyes with uveitis having cataract surgery: Long-term follow-up: *J Cataract Refract Surg*. 2011;37(1):104-112. doi:10.1016/j.jcrs.2010.07.038
148. Roesel M, Heinz C, Heimes B, Koch JM, Heiligenhaus A. Uveal and capsular biocompatibility of two foldable acrylic intraocular lenses in patients with endogenous uveitis-a prospective randomized study. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(11):1609-1615. doi:10.1007/s00417-008-0886-4
149. Vasavada A, Desai J. Primary posterior capsulorhexis with and without anterior vitrectomy in congenital cataracts. *J Cataract Refract Surg*. Published online 1997. doi:10.1016/S0886-3350(97)80048-X
150. Lundvall A, Zetterström C. Cataract extraction and intraocular lens implantation in children with uveitis. *Br J Ophthalmol*. 2000;84(7):791-793. doi:10.1136/bjo.84.7.791
151. Pålsson S, Nyström A, Sjödell L, Jakobsson G, Byhr E, Andersson Grönlund M, Zetterberg M. Combined phacoemulsification, primary intraocular lens implantation, and pars plana vitrectomy in children with uveitis. *Ocul Immunol Inflamm*. 2015;23(2):144-151. doi:10.3109/09273948.2014.883546
152. Li J, Heinz C, Zurek-Imhoff B, Heiligenhaus A. Intraoperative intraocular triamcinolone injection prophylaxis for post-cataract surgery fibrin formation in uveitis associated with juvenile idiopathic arthritis. *J Cataract Refract Surg*. 2006;32(9):1535-1539. doi:10.1016/j.jcrs.2006.04.018
153. Akella M, Ram J, Suri D, Gupta A, Agarwal A, Jinagal J, Gupta G, Singh S, Gupta V, Aggarwal K. Safety and efficacy of dexamethasone implant along with phacoemulsification and intraocular lens implantation in children with juvenile idiopathic arthritis associated uveitis. *Indian J Ophthalmol*. Published online 2018. doi:10.4103/ijo.ijo_713_18
154. Chu CJ, Dick AD, Johnston RL, Yang YC, Denniston AK, UK Pseudophakic Macular Edema Study Group. Cataract surgery in uveitis: a multicentre database study. *Br J Ophthalmol*. 2017;101(8):1132-1137. doi:10.1136/bjophthalmol-2016-309047
155. Sijssens KM, Rothova A, Berendschot TTJM, de Boer JH. Ocular hypertension and secondary glaucoma in children with uveitis. *Ophthalmology*. 2006;113(5):853-859.e2. doi:10.1016/j.ophtha.2006.01.043
156. Skarin A, Elborgh R, Edlund E, Bengtsson-Stigmar E. Long-term follow-up of patients with uveitis associated with juvenile idiopathic arthritis: A cohort study. *Ocul Immunol Inflamm*. Published online 2009. doi:10.1080/09273940802650398
157. Kalogeropoulos D, Sung VC. Pathogenesis of uveitic glaucoma. *J Curr Glaucoma Pract*. 2018;12(3):125-138. doi:10.5005/jp-journals-10028-1257
158. Coppens G, Stalmans I, Zeyen T, Casteels I. The safety and efficacy of glaucoma medication in the pediatric population. *J Pediatr Ophthalmol Strabismus*. 2009;46(1):12-18. doi:10.3928/01913913-20090101-05
159. Giampani Junior J, Borges-Giampani AS, Carani JCE, Oltrogge EW, Susanna Junior R. Efficacy and safety of trabeculectomy with mitomycin C for childhood glaucoma: a study of results with long-term follow-up. *Clinics*. 2008;63(4):421-426. doi:10.1590/S1807-59322008000400002
160. Anand N. Deep sclerectomy with mitomycin C for glaucoma secondary to uveitis. *Eur J Ophthalmol*. 2011;21(6):708-714. doi:10.5301/EJO.2011.6487
161. Eksioglu U, Yakin M, Sungur G, Satana B, Demirok G, Balta O, Ornek F. Short- to long-term results of Ahmed glaucoma valve in the management of elevated intraocular pressure in patients with pediatric uveitis. *Can J Ophthalmol*. 2017;52(3):295-301. doi:10.1016/j.jcjo.2016.11.015
162. Heinz C, Koch JM, Heiligenhaus A. Transscleral diode laser cyclophotocoagulation as primary surgical treatment for secondary glaucoma in juvenile idiopathic arthritis: high failure rate after short term follow up. *Br J Ophthalmol*. 2006;90(6):737-740. doi:10.1136/bjo.2005.085936
163. Iwao K, Inatani M, Seto T, Takihara Y, Ogata-Iwao M, Okinami S, Tanihara H. Long-term outcomes and prognostic factors for trabeculectomy with mitomycin c in eyes

with uveitic glaucoma: A retrospective cohort study. *J Glaucoma*. 2014;23(2):88-94. doi:10.1097/IJG.0b013e3182685167
164. Scuderi G, Iacovello D, Pranno F, Plateroti P, Scuderi L. Pediatric glaucoma: a literature's review and analysis of surgical results. *BioMed Res Int*. 2015;2015:1-8. doi:10.1155/2015/393670
165. Watson PG, Barnett F. Effectiveness of trabeculectomy in glaucoma. *Am J Ophthalmol*. Published online 1975. doi:10.1016/0002-9394(75)90745-X
166. Landers J, Martin K, Sarkies N, Bourne R, Watson P. A twenty-year follow-up study of trabeculectomy: risk factors and outcomes. *Ophthalmology*. 2012;119(4):694-702. doi:10.1016/j.ophtha.2011.09.043
167. Holló G. Wound healing and glaucoma surgery: modulating the scarring process with conventional antimetabolites and new molecules. In: Bettin P, Khaw PT, eds. *Developments in Ophthalmology*. Vol 59. S. Karger AG; 2017:80-89. doi:10.1159/000458488
168. Wilkins M, Indar A, Wormald R. Intraoperative mitomycin C for glaucoma surgery. *Cochrane Database Syst Rev*. 2005;(4):CD002897. doi:10.1002/14651858.CD002897.pub2
169. Yamanaka O, Kitano-Izutani A, Tomoyose K, Reinach PS. Pathobiology of wound healing after glaucoma filtration surgery. *BMC Ophthalmol*. Published online 2015. doi:10.1186/s12886-015-0134-8
170. Cunliffe IA, Richardson PS, Rees RC, Rennie IG. Effect of TNF, IL-1, and IL-6 on the proliferation of human Tenon's capsule fibroblasts in tissue culture. *Br J Ophthalmol*. Published online 1995. doi:10.1136/bjo.79.6.590
171. Cvenkel B, Kopitar AN, Ihan A. Inflammatory molecules in aqueous humour and on ocular surface and glaucoma surgery outcome. *Mediators Inflamm*. Published online 2010. doi:10.1155/2010/939602
172. Lukowski ZL, Min J, Beattie AR, Meyers CA, Levine MA, Stoller G, Schultz GS, Samuelson DA, Sherwood MB. Prevention of ocular scarring after glaucoma filtering surgery using the monoclonal antibody LT1009 (Sonepcizumab) in a rabbit model. *J Glaucoma*. Published online 2013. doi:10.1097/IJG.0b013e31822e8c83
173. Turgut B, Eren K, Demir T, Kobat S, Akin M. Topical infliximab for the suppression of wound healing following experimental glaucoma filtration surgery. *Drug Des Devel Ther*. 2014;8:421-429. doi:10.2147/DDDT.S63320
174. Almobarak FA, Alharbi AH, Morales J, Aljadaan I. Intermediate and long-term outcomes of mitomycin C–enhanced trabeculectomy as a first glaucoma procedure in uveitic glaucoma. *J Glaucoma*. 2017;26(5):478-485. doi:10.1097/IJG.0000000000000653
175. Saeedi OJ, Jefferys JL, Solus JF, Jampel HD, Quigley HA. Risk factors for adverse consequences of low intraocular pressure after trabeculectomy. *J Glaucoma*. Published online 2014. doi:10.1097/IJG.0000000000000008
176. Mercieca K, Steeples L, Anand N. Deep sclerectomy for uveitic glaucoma: Long-term outcomes. *Eye Basingstoke*. Published online 2017. doi:10.1038/eye.2017.80
177. Ramdas WD, Pals J, Rothova A, Wolfs RCW. Efficacy of glaucoma drainage devices in uveitic glaucoma and a meta-analysis of the literature. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(1):143-151. doi:10.1007/s00417-018-4156-9
178. Bohnsack BL, Freedman SF. Surgical outcomes in refractory uveitic glaucoma. *J Am Assoc Pediatr Ophthalmol Strabismus*. Published online 2012. doi:10.1016/j.jaapos.2011.12.010
179. Liang F, Terrada C, Ducos de Lahitte G, Quartier P, Lehoang P, Thorne JE, Bodaghi B. Foveal serous retinal detachment in juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm*. 2016;24(4):386-391. doi:10.3109/09273948.2015.1012297
180. García-De-Vicuña C, Díaz-Llopis M, Salom D, Bou R, Díaz-Cascajosa J, Cordero-Coma M, Ortega G, Ortego-Centeno N, Suarez-De-Figueroa M, Cruz-Martínez J, Fonollosa A, Blanco R, García-Aparicio ÁM, Benítez-Del-Castillo JM, Antón J. Usefulness of adalimumab in the treatment of refractory uveitis associated with juvenile idiopathic arthritis. *Mediators Inflamm*. 2013;2013:1-6. doi:10.1155/2013/560632
181. Pato E, Muñoz-Fernández S, Francisco F, Abad MA, Maese J, Ortiz A, Carmona L, Uveitis Working Group from Spanish Society of Rheumatology. Systematic review on the effectiveness of immunosuppressants and biological therapies in the treatment of

autoimmune posterior uveitis. *Semin Arthritis Rheum*. 2011;40(4):314-323. doi:10.1016/j.semarthrit.2010.05.008
182. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group, Kempen JH, Altaweel MM, Drye LT, Holbrook JT, Jabs DA, Sugar EA, Thorne JE. Benefits of systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, and panuveitis : Fifty-four-month results of the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up. *Ophthalmology*. 2015;122(10):1967-1975. doi:10.1016/j.ophtha.2015.06.042
183. Kenawy N, Cleary G, Mewar D, Beare N, Chandna A, Pearce I. Abatacept: A potential therapy in refractory cases of juvenile idiopathic arthritis-associated uveitis. *Graefes Arch Clin Exp Ophthalmol*. Published online 2011. doi:10.1007/s00417-010-1523-6
184. Venkatesh P, Abhas Z, Garg S, Vohra R. Prospective optical coherence tomographic evaluation of the efficacy of oral and posterior subtenon corticosteroids in patients with intermediate uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2007;245(1):59-67. doi:10.1007/s00417-006-0378-3
185. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, Nussenblatt RB, Stiehm ER, Tessler H, Van Gelder RN, Whitcup SM, Yocum D. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2000;130(4):492-513. doi:10.1016/S0002-9394(00)00659-0
186. Cabrera M, Yeh S, Albini TA. Sustained-release corticosteroid options. *J Ophthalmol*. 2014;2014:1-5. doi:10.1155/2014/164692
187. Arcinue CA, Cerón OM, Foster CS. A comparison between the fluocinolone acetonide (Retisert) and dexamethasone (Ozurdex) intravitreal implants in uveitis. *J Ocul Pharmacol Ther*. 2013;29(5):501-507. doi:10.1089/jop.2012.0180
188. Parekh A, Srivastava S, Bena J, Albini T, Nguyen QD, Goldstein DA. Risk factors associated with intraocular pressure increase in patients with uveitis treated with the fluocinolone acetonide implant. *JAMA Ophthalmol*. 2015;133(5):568. doi:10.1001/jamaophthalmol.2015.51
189. Sen HN, Abreu FM, Louis TA, Sugar EA, Altaweel MM, Elner SG, Holbrook JT, Jabs DA, Kim RY, Kempen JH. Cataract surgery outcomes in uveitis. *Ophthalmology*. 2016;123(1):183-190. doi:10.1016/j.ophtha.2015.09.022
190. Jaffe GJ, Foster CS, Pavesio CE, Paggiarino DA, Riedel GE. Effect of an injectable fluocinolone acetonide insert on recurrence rates in chronic noninfectious uveitis affecting the posterior segment: twelve-month Results. *Ophthalmology*. 2019;126(4):601-610. doi:10.1016/j.ophtha.2018.10.033
191. Lange C, Feltgen N, Junker B, Schulze-Bonsel K, Bach M. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol*. 2009;247(1):137-142. doi:10.1007/s00417-008-0926-0
192. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4(4):543-547. doi:10.1002/sim.4780040416
193. Machin D, Cheung YB, Parmar MKB, Parmar MKB. *Survival Analysis: A Practical Approach*. 2nd ed. Wiley; 2006.
194. Benucci M, Li Gobbi F, Meacci F, Manfredi M, Infantino M, Severino M, Testi S, Sarzi-Puttini P, Ricci C, Atzeni F. Antidrug antibodies against TNF-blocking agents: correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins. *Biol Targets Ther*. 2015;9:7-12. doi:10.2147/BTT.S69606
195. Marino A, Real-Fernández F, Rovero P, Giani T, Pagnini I, Cimaz R, Simonini G. Anti-adalimumab antibodies in a cohort of patients with juvenile idiopathic arthritis: incidence and clinical correlations. *Clin Rheumatol*. 2018;37(5):1407-1411. doi:10.1007/s10067-018-4057-7
196. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, Unnebrink K, Anderson JK. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. *Arthritis Care Res*. 2015;67(11):1503-1512. doi:10.1002/acr.22657